Clinical Medicine

Original Articles for September, 1959

Monoamine Oxidase Inhibitors: A Symposium

for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

Miltown®

meprobamate (Wallace)

CM-9298

WALLACE LABORATORIES / *New Brunswick, N. J.*

Clinical Medicine

Vol. VI, No. 9

CONTENTS FOR SEPTEMBER, 1959

NOW SHE CAN COOK BREAKFAST AGAIN

...WHEN YOU PRESCRIBE

MORNIDINE™

(BRAND OF PIPAMAZINE)

A new drug with specific effectiveness in nausea and vomiting of pregnancy, Mornidine eliminates the ordeal of morning sickness.

With its selective action on the vomiting center, or the medullary chemoreceptor "trigger zone," Mornidine possesses the advantages of the phenothiazine drugs without unwanted tranquilizing activity.

Doses of 5 to 10 mg., repeated at intervals of six to eight hours, provide excellent relief all day. In patients who are unable to retain oral medication when first seen, Mornidine may be administered intramuscularly in doses of 5 mg. (1 cc.).

Mornidine is supplied as tablets of 5 mg. and as ampuls of 5 mg. (1 cc.).

G. D. Searle & Co., Chicago 80, Ill.
Research in the Service of Medicine.

TABLE OF CONTENTS *(Continued)*

Symposium on Monoamine Oxidase Inhibitors

Original Articles

TABLE OF CONTENTS *(Continued)*

Clinical Note

Current Literature

Fast, *potentiated* attack on...

URINARY INFECTION

In just a matter of minutes URISED provides four way antibacterial action to relieve genitourinary irritation and smooth muscle spasm . . . to reduce pus cell count . . . to promote mucosal healing.

In just a matter of minutes URISED soothes ureteral and urethral spasticity... alleviates discomfort and irritation . . . restores normal urinary tonus and function.

In cystitis, urethritis, pyelitis, pyelonephritis, ureteritis, acute and chronic infections . . . try this dual-powered, double-fast attack on the primary causes of urinary pain, burning, urgency, dysuria and frequency.

samples and literature to physicians on request

urised

SUPPLIED: Bottles of 100, 1000 and 2000 tablets.

CHICAGO PHARMACAL COMPANY / CHICAGO, ILLINO

TABLE OF CONTENTS *(Continued)*

Case Reports

Briefs: Medical

Briefs: Surgical

TABLE OF CONTENTS *(Continued)*

Briefs: Surgical

Briefs: Therapeutic

Briefs: Obstetric

Departments

MANUSCRIPTS should be addressed to The Editor, *Clinical Medicine*, P. O. Box M, Winnetka, Illinois. Manuscripts accepted only with the understanding that they are contributed exclusively to *Clinical Medicine*. Manuscripts should be typed double or triple-spaced, on one side of the paper only. Drawings or photographs will be reproduced at no cost to the author. Bibliographic references should be kept to a minimum.

REPRINTS Authors will be furnished reprints at cost. Manuscripts, when accepted, become the exclusive property of *Clinical Medicine*.

ORIGINAL ARTICLE

Home Care of Psychiatric Patients In the Netherlands

This system, using the services of psychiatrists and social workers on call 24 hours daily, promises success

JAMES M. NORTHINGTON, M.D., *Editor-in-Chief*

It has been said that the care of psychiatric patients in the United States is both unsatisfactory and excessively costly. I believe there will be little dissent from those who have given the subject any thought and study. This state of affairs is due largely to the fact that such care, at public expense, is provided only as institutional treatment.

Although the administration of certain drugs made available only in the past dozen years has greatly increased the discharge rate among patients in hospitals for the mentally ill, there remains great need for means of achieving better results without stigmatizing patients and families, and at far less cost.

A Minnesota psychiatrist[1] was so impressed with a system that he saw in Europe that he outlined its organization and operation.

This system was gradually developed in Amsterdam after World War I. It is based on the theory that cure of rehabilitation can be accomplished *only in society itself*. In the home, study of the conflict is made in its proper setting. In Amsterdam there are 22 out-patient treatment centers at which ambulatory patients can receive specialized therapy, each hav-

1. Baars, C. W., *Minnesota Med.*, 42:92-99,1959.

ing one psychiatrist among its specialists. There are two treatment centers for psychotherapy, operating with public grants. The two general hospitals that admit psychiatric patients together have 300 beds in addition to large out-patient departments.

The mental health service usually consists of 12 psychiatrists, always has four or five psychiatrists in training, and 25 social workers. Two psychiatrists and two social workers are assigned to each of the six sectors into which the city has been divided. They work on a rotating 24 hour schedule. From 6:00 p.m. until 8:00 a.m., and on week-ends, there is one psychiatrist on duty all the time. On an average, 3000 adults are under supervision, most of them living in their own, some in foster, homes. The service receives an average of 250 inquiries daily; some are handled by telephone through quick reference to case records; others require a home visit by the psychiatrist and his social worker assistant.

When an official or private party calls the center to report a person not known to the service as considered mentally ill, the psychiatrist on duty is bound to go out and investigate.

The first "on-the-spot" contact with the patient must be made by a psychiatrist, because the responsibility for and the authority to back this decision, can be assumed only by the expert physician. Such a service with too many social workers relative to the number of psychiatrists lowers its effectiveness to the point of uselessness. One psychiatrist in this service has been found to be more effective than all the personnel of a 50-bed ward.

The patient must be educated to accept society, society to accept the patient. A psychiatrist demonstrates by his own behavior that by treating the patient with understanding and honesty, especially honesty, and without showing fear or using force, tensions may be reduced to such a point that the patient becomes manageable. Such an occurrence leaves a deep impression on those who witness it and is apt to change their concept of mental illness more than many lectures or newspaper articles.

The success of this domicilary system in Amsterdam and other Dutch communities over a period of 30 years has been such that it warrants close study and investigation for applicability in various U.S. communities.

Although the need for such a service is most pressing in the larger cities, it could be established in rural communities. The service must be ready to meet every personal emergency at any time; there must be no bureaucratic delay between the time a problem comes to the attention of the service and the time when first contact is made by a psychiatrist.

It is immaterial whether such a service be set up by state, county, city or private bodies or organizations. It may be run by one hospital or by a group of hospitals; or private organizations and voluntary societies may unite to set up such a service. In the beginning it would be best to limit treatment to one or two groups of patients, e.g., those suffering from alcoholism, suicidal tendencies, drug addiction, or disturbed geriatric patients. The speed of development will depend on its initial success with patients, cooperation from other organizations, and time to overcome opposition from families, hospital administrators, psychiatrists in private practice, and others.◀

ORIGINAL ARTICLE

The Role of Beta-phenylisopropyl Hydrazine (JB-516) in Clinical Medicine

Preliminary reports indicate that this drug produces as effective results as electroshock, even in severe depressions

JULIUS POMERANZE, M.D.,* and LEONARD CAMMER,† M.D.,
New York, New York

Emotional disturbance in a patient is most frequently manifested either as agitation and anxiety or as depression. The 50,000,000-odd tranquilizer prescriptions written annually afford a rough idea of the prevalence of anxiety. While the incidence of depression is less easily estimated, it is generally conceded to be higher than anxiety, and many regard depression as the commonest of all emotional ailments.

In recent months, a number of reports on monoamine oxidase (MAO) inhibitors have appeared which seem to promise a new era for the depressed patient comparable to that initiated by tranquilizers for the tense, agitated, anxious ones.

Preliminary reports from psychiatric hospitals have indicated efficacy comparable to that of electroshock therapy (EST) even in the most severe forms of depression. In the hospital milieu, there is a vast difference between the severely agitated patient and the severely depressed one. Where the first may disrupt an entire ward, the latter may go unnoticed for days at a time. One is noisy, demand-

*Director of Research, †Director, Gracie Square Hospital, New York.

ing and aggressive; the other withdraws in silence and asks only to be left alone. The psychiatrist, recognizing both patterns of behavior as evidence of serious mental and emotional disturbance, is as eager to dispel the silence of the depressed patient as the noise and hyperactivity of the agitated one. Nevertheless, the wildly disturbed patient who becomes tranquil through the action of a pharmacologic agent must be a more dramatic testimonial to its efficacy than the silent patient who begins to speak normally.

In daily practice, where neither agitation nor depression assumes such extreme proportions, the agitated patient is still more assertive, more demanding, and more obviously in need of treatment. The mildly depressed patient may give little or no indication of his condition beyond a tendency to sit still, answer in muffled monosyllables, and utter an occasional sigh.

Moreover, depression is frequently masked behind a multitude of secondary somatic symptoms which may divert the physician from the primary emotional defect. Anxiety itself may mask an underlying depression, or depression may be initiated by a wholly realistic environmental situation which the patient is unequipped to meet realistically. In such cases, the immediate reaction seems normal and fully justified by the events. It is only when the depression becomes prolonged and intensified rather than ameliorated by time that the emotional defect becomes evident.

In short, depression is less intrusive, less dramatic, and less easily diagnosed than anxiety or agitation. Though it is widely prevalent it is apt to attract little attention unless one is alerted to its manifestations. Paradoxically, this very lack of interest is depression as a clinical state increases the physician's responsibility for recognizing it in all its protean forms, and treating it with the same concentrated effort he would apply to the more overt forms of emotional disturbance. The popular press will give fewer headlines to the antidepressants than it did to the tranquilizers. At the same time, though, the benefits to be derived from an effective mood-elevating agent may be far greater. The clinically useful properties of the monoamine oxidase inhibitors are notable and clearly warrant both discussion and investigation.

Iproniazid, the first monoamine oxidase inhibitor to be used deliberately for its antidepressant properties, was studied originally as an anti-tuberculosis agent. During clinical trials a marked antidepressant effect attributable to the drug was noted, which effect was confirmed in studies of psychiatrically depressed patients.[1,2] While psychic stimulation had previously been noticed from the use of structurally similar compounds such as ephedrine and the amphetamines, these were known to be weak inhibitors of monoamine oxidase, and other mechanisms of action were needed to explain their effects. With iproniazid, however, the suppression of monoamine oxidase was marked and the concurrent elevation of mood was ascribed to this pharmacologic action.

Because iproniazid's antidepressant properties were often accompanied by evidence of liver toxicity, new compounds were sought in the hope of increasing specificity of action and re-

1. Loomer, H. P., et al.: *Psychiatric Research Reports*, 8:129,1957.
2. Orland, I. & Comas, N. L.: *J. Dis. Nerv. Syst.*, 19:182,1958.

ducing side effects. Among these is β-phenylisopropyl hydrazine (JB-516)*.

PRELIMINARY STUDIES

Thirty-three ambulant psychiatric patients were studied over a 3-month period. The patients ranged in age from 21 to 71 years and all exhibited depression of varying degrees and types. Marked improvement was noted in 18 patients, amelioration of symptoms in 10 more. Results of toxicity studies run concurrently in the patients were negative. These included complete liver profiles, hemograms, urine examinations, and electroencephalograms. Elevation of mood, diminution of confusion and increased alertness and ability to maintain work and social adjustments were characteristic of the beneficial effects observed.[3]

Similarly encouraging results were reported following an 8-month study of 41 depressive and psychoneurotic patients treated with JB-516.[4] Results were considered comparable to those which would have been expected of EST in endogenous depressions, and far superior to EST in reactive depressions. In over half of the group, improvement, "dramatic, complete, and lasting," was obtained by a therapy simpler and far more acceptable to the patient than EST.

In another study of psychiatric patients, substantial improvement was noted in 20 of 25 patients, including complete remission of all symptoms of depression in 15. Twenty of these patients had previously received EST and the JB-516 regimen was instituted following relapse into moderate to severe depressive states. While the response to JB-516 was less sudden than that associated with electroshock, it appeared more sustained and uncomplicated by confusional-amnestic syndromes, such as frequently follow EST.[5]

While these reports clearly delineate a potent psychoactive agent, none of them deals specifically with the very common mild-to-moderate depression seen often in private, non-psychiatric patients for whom EST would rarely be considered.

Since the ultimate value of almost any drug depends on the therapeutic parameters established for it in private practice, a systematic evaluation of JB-516 in these less severe depressions and asthenias of daily practice was started.

METHOD OF STUDY

Seventy-nine patients were studied, none of whom were overtly psychotic. In general, depression could be traced to problems which had evoked an abnormally intense or prolonged emotional response in unduly susceptible patients. Of the total group, 46 were geriatric patients, four of whom were hospitalized. Enforced retirement, fear of impending disease, poverty, physical deterioration, or removal to chronic disease hospitals or homes for the aged, were prominent factors contributing to the depressions of these patients.

Eighteen patients were chronically asthenic following convalescence from surgery, or an attack of an infectious or other medical disease. The remaining 15 presented a variety of physical complaints with mental and emotion-

*Catron®, Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

3. Agin, H. V.: The Use of JB-516 in Psychiatry, Conf. on Amine Oxidase Inhibitors, New York Acad. of Sciences, Nov. 20-22,1958.

4. Kinross-Wright, J. V.: Panel Discussion of Psychic Energizers, in A Pharmacologic Approach to the Study of the Mind, Charles C. Thomas, Springfield, Ill., 1959, in press.

5. Bercel, N. A.: Panel Discussion of Psychic Energizers, ibid.

al symptoms in the background. This confused clinical picture was particularly common in women, whose recurrent attacks of depression were customarily related to irregularities in the menstrual cycle. While the pattern of depression masked by somatic complaints has become familiar in theory to most physicians, in practice it is probably still responsible for more referrals, consultations, and unnecessary diagnostic studies than any other single emotional complex.

Therapeutic response in the study group was compared to that obtained with a placebo in 13 patients.

Since full details of the evaluation are available elsewhere, results and methodology will be described here only in outline.[6,7] The aims of the study were:

1. To determine the therapeutic potential of JB-516 in private, nonpsychiatric, medical patients.

2. To establish a practical, effective dosage schedule.

3. To determine the extent and character of side effects.

On the basis of a preliminary dosage titration, 12.5 mg. per day was selected as the optimum. At higher dosages muscular weakness and an occasional tremor, particularly of the eyelid, was seen. Though several patients complained of early morning wakefulness on a dose of 25 mg. per day, at the selected clinical dose level, side effects were minimal and no evidence of toxicity was observed in any patient, including 2 who were treated for a full year and 18 for six months. Maintenance dosage was half the therapeutic, or the same at intervals of two or more days. Clinical improvement was maintained in a few patients by 12.5 mg. every four days.

The typical response to 12.5 mg. of JB-516 per day was a slowly achieved, smoothly maintained elevation of mood, without euphoria, hyperactivity, appetite suppression, or sympathomimetic side effects. While the mood elevation itself was vaguely reminiscent of that associated with amphetamines, the total effect was quite dissimilar.

The depressed patients who responded to the drug gradually achieved a sane, sensible, orderly, and controlled behavior, remarkable only when contrasted to the depression it replaced.

There were no sudden or dramatic shifts in mood. The symptoms of depression were dissipated as gradually and imperceptibly as if neither the drug nor the emotional problem itself had existed.

At the same time, the lack of response in the placebo-treated group left no doubt that the improvement observed was attributable to drug action.

The usefulness of the compound was obvious in the asthenics and in those patients requiring an emotional buffer to sustain them until overwhelming problems could be resolved or faced realistically. While some amelioration of symptoms occurred in the institutionalized geriatic patients studied, response in this group was less satisfactory than in the ambulatory patients.

Obviously, neither this personal experience, nor the reports of those who have studied this agent in psychiatric practice, are sufficient to de-

6. Pomeranze, J.: Experience with JB-516 and other Psychochemicals in Clinical Practice, Conf. on Amine Oxidase Inhibitors, New York Acad. of Science, Nov. 20-22, 1958.

7. Pomeranze, J.: Comparative Clinical Pharmacology of JB-516 and Related Compounds, in A Pharmacologic Approach to the Study of the Mind, Charles C. Thomas, Springfield, Ill., 1959, in press.

fine the range of its activity and clinical usefulness precisely. Nevertheless, it is obvious that JB-516 is an unusually effective pharmacologic agent with antidepressant properties well beyond the range of the conventional psychic stimulants and euphorient drugs that have been employed until now in the treatment of depression.

The lack of drama in patient response is deceptive, and poses a particular problem for the clinical investigator. The physician seeing his patient at intervals of a week or more may well be in a better position to detect his response than the meticulous observer who seeks to isolate each minute detail of the patient's progress. In either case, however, the physician is likely to need a good memory or a good set of records if he hopes to judge response adequately.

A second problem in the use of JB-516, common to all psychoactive drugs of this order, and commented on by many investigators since the introduction of tranquilizers, is the temptation to the physician to abdicate his role in treating the patient merely because an effective adjunct to treatment has been made available to him.

It is essential to realize that not one of the psychoactive agents in use today is capable of resolving the deep-seated emotional problems that underlie a patient's clinically detectable agitation or depression.

As a temporary expedient, a drug such as JB-516 can produce something very like a cure for depression. If, for example, the patient is depressed by the threat of losing his job, the drug may insulate him from his concern until the problem is resolved in one way or another. After the problem has ceased to be a threat, and the drug is withdrawn, the patient continues to maintain his improvement, and to all outward appearances, his depression is cured. The next crisis that arises may plunge him into a relapse. Whenever such a problem arises, the physician can blame himself rather than the drug for permitting it to happen. While many patients are beyond the reach of psychotherapy, those who are not should not be denied it merely because their emotions seem to be adequately controlled by drug action. The defect that permitted the initial emotional breakdown will persist until it is rooted out by the physician or by the patient himself. Psychoactive agents have proven themselves valuable adjuncts to psychotherapy, but this critically important asset will be wasted if the physician is unwilling or unprepared to capitalize on it.

SIDE EFFECTS

As to side effects, several investigators have reported orthostatic hypotension in patients treated with JB-516, suggesting clinical application in the treatment of hypertension. Hypotension was not observed by us, despite careful observation of the patients for evidence of any form of untoward reaction, and despite an initial dose level of 75 mg. per day during the period prior to establishing an optimal clinical dose at one-sixth of this amount.

While severe liver toxicity has not been observed, it cannot be ruled out as a potential hazard without far wider use of the drug. Transient increases in several tests of liver function have been reported,[8,9] and,

8. Greenblatt, I. J.: Panel Discussion of Psychic Energizers, ibid.
9. Agin, H. V.: Panel Discussion of Psychic Energizers, ibid.

though the patients studied did not become jaundiced, any patient receiving a potent pharmacologic agent of this type will require careful observation until the range of its activity is better understood.

USE IN ANGINA PECTORIS

Finally, in addition to its antidepressant activity, the drug possesses two striking properties with potentially widespread clinical value which require comment. The first of these is a marked antianginal effect. Substantial degrees of relief in patients with angina pectoris who had been treated with iproniazid have been reported.[10,11] Side effects severely limited the use of the drug, however, and it never attained widespread use in this indication. The possibility that JB-516 might duplicate the antianginal effects of iproniazid without its side effects, was, of course, considered at an early date.

A study of 31 patients with severe angina pectoris treated with JB-516 resulted in "marked improvement", consisting of complete cessation of pain and ability of the patient to discontinue nitroglycerin in 12 patients.[12] In 11 more there was notable improvement, although the patients could not dispense with nitroglycerin. While recognizing the preliminary nature of the study, the investigators consider the drug to be "of great value in the treatment of severe angina pectoris". Because of the improved mood and freedom from pain achieved, the investigators felt it essential to caution the patient against overexertion, since the basic cardiac defect is not altered by the action of JB-516.

10. Cesarman, I.: *Arch. Inst. cardiol. Mexico*, 27: 563,1957.
11. Cossio, P.: *Am. Heart J.*, 56:113,1958.
12. Kennamer, R., & Prinzmetal, M.: *Am. J. Cardiol.*, 111:542,1959.

In our experience with JB-516 in patients in angina pectoris, the drug has been used exclusively in patients who were almost totally disabled by the condition and unresponsive to other therapy. In this virtually hopeless group, the drug has produced significant reduction in frequency and severity of the individual attacks. This is an area of extreme need where the effectiveness of the drug has been dramatic.

EFFECT ON RHEUMATOID ARTHRITIS

An equally unusual aspect of the drug has been its effect in rheumatoid arthritis. In an evaluation in 30 patients with rheumatoid arthritis, not only the characteristic elevation of mood, but also an increase in strength, a lessening of musculoskeletal pain, and significant reduction in joint swelling and tenderness was observed.[13]

Although we have not yet studied the clinical effects in this indication, short-term laboratory studies have been initiated to determine whether changes in immunologic response of the type seen with corticosteroids are associated with JB-516.[14] While no such changes have been observed, these laboratory findings are not incompatible with the clinical improvement reported by others. They merely indicate that such improvement probably derives from the central effects of the drug and cannot be attributed to alterations in the immunologic pattern of the patient.

In the hands of many investigators, potent pharmacologic activity of JB-516 has been demonstrated in areas with wide applications to clinical

13. Scherbel, A. L., & Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conf. on Amine Oxidase Inhibitors, New York Acad. of Sciences, Nov. 20-22, 1958.
14. Hall, A. P., et al.: *N. Eng. J. Med.*, 258:781,1958.

medicine. Its antidepressant properties have proved valuable in an important segment of the psychiatrically disturbed population, both institutionalized and ambulatory. Its usefulness has been further confirmed in the milder types of depression seen in clinical practice. Investigators have demonstrated its value in rheumatoid arthritis and angina pectoris. While these may appear to be paradoxical indications for a psychoactive agent, the relationship becomes less incongruous when one speculates on the action of the drug in terms of its inhibition of monoamine oxidase, an enzyme related to metabolic function throughout the body.

Depression may arise concomitantly with any disease process, and the effect of the drug in allaying this depression may also help to explain its efficacy in conditions which appear to be clinically unrelated.◀

Carcinoid Syndrome

The symptoms and signs produced by carcinoid tumors are protean and involve many of the major organ systems. Many, if not all, of the various presenting features of the syndrome may be attributed to one basic chemical, 5-hydroxytryptamine, or serotonin. Correlation of the pathophysiology with clinical expressions is well demonstrated by the carcinoid syndrome. Primary carcinoid tumors (argentaffinomas) may arise in any part of the gastro-intestinal tract, including the gall-bladder and have been reported in teratomata of the ovary and testes when these tumors contain gastro-intestinal tissue.

The most characteristic symptom is paroxysmal cutaneous flushing, especially of the face. It may persist for as long as 10 minutes. The central portions fade first, progressing peripherally in resulting serpiginous patterns. As the flushing becomes more chronic, telangiectases and a persistent cyanosis of the face develop. The scleras are reddened. The appearance is that of polycythemia vera, without the hematologic changes and clubbing of the fingers.

Diarrhea, often the first sign of the disease, as a rule continues throughout the course: watery movements per day may reach 20 to 30 with intermittent abdominal pain and borborygmi. Pulmonary symptoms are asthma-like with dyspnea and respiratory stridor.

As end results, the tricuspid and pulmonary valves become vascularized and sclerotic, thickened and distorted. The sclerotic tissue may extend to form well defined cushions overlying the intima of the pulmonary artery or the lining of the right atrium. There may also be patches of endocardial fibrosis elsewhere in the right heart, of dense, acellular collagenous tissue with occasional collections of round cells. The mitral and aortic valves are seldom affected.

Some observers believe the cardiac changes to be the result of a nutritional deficiency, specifically of tryptophane. Using radioactive tryptophane, it was found, in one case, that the quantity of 5-hydroxyindole acetic acid in the urine varied according to the quantity of tryptophane fed, and that the intake of tryptophane necessary to maintain nitrogen balance was 500 mg., thrice the normal requirement.

Pastras, T., *J. Med. Soc. New Jersey*, 56:160-162, 1959.

cold 'miseries'

stuffed and
running noses,
fever,
headache,
muscular discomfort

Triaminicin®

provide prompt relief with this logical formulation

TRIAMINIC for more complete, more effective relief from nasal and paranasal congestion because of systemic transport to all respiratory membranes – without drawbacks of topical therapy[1,2,3]

plus A-P-C for classical control of headache, fever and muscular discomfort, commonly encountered in respiratory ills

plus VITAMIN C to help prevent or correct a deficiency which may develop due to anorexia or increased requirements caused by infection[4]

plus ALUMINUM HYDROXIDE GEL for superior gastric tolerance through antacid action

1. Lhotka, F. M.: Illinois M. J. 112:259 (Dec.) 1957.
2. Fabricant, N. D.: E.E.N.T. Monthly 37:460 (July) 1958.
3. Farmer, D. F.: Clin. Med. 5:1183 (Sept.) 1958.
4. U. S. Disp., 25th Ed. J. B. Lippincott, Philadelphia, 1955, p. 119.

Each TRIAMINICIN Tablet provides:

TRIAMINIC®	50 mg.
(phenylpropanolamine HCl	25 mg.
pheniramine maleate	12.5 mg.
pyrilamine maleate	12.5 mg.)
Acetylsalicylic acid	(3½ gr.) 225 mg.
Phenacetin	(2½ gr.) 150 mg.
Caffeine	(½ gr.) 30 mg.
Ascorbic acid	50 mg.
Aluminum hydroxide gel (dried)	180 mg.

Dosage: 1 Triaminicin tablet every 3 to 4 hours.

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska

ORIGINAL ARTICLE

Comparative Pharmacology of Hydrazine Analogues Clinically Useful as Monoamine Oxidase Inhibitors

A review of the pharmacologic properties of hydrazine analogues useful in inhibiting monoamine oxidase

AKIRA HORITA,* Ph.D., *Seattle, Washington*

The amine oxidases are enzymes which oxidatively deaminate amines according to the general equation:

$$R\text{-}CH_2\text{-}NH_3 + 0_2 + H_20 = R\text{-}CH0 + NH3 + H_20_2$$

Deamination of monoamines such as serotonin, norepinephrine, tryptamine, tyramine, and butylamine[1,2] is accomplished by monoamine oxidase (MAO), which is widely distributed in animal tissues, particularly brain, liver, kidney and intestine.

Serotonin and norepinephrine are formed by decarboxylation of their amino acid precursors. In brain tissue both are stored in definite concentrations. While in this stored form, they cannot be deaminated by monoamine oxidase, nor can they exert their usual physiologic effects. It is believed that under normal conditions, there is a constant release of the stored amines to their free, physiologically active forms, which are susceptible to enzymatic degradation. A balance presumably exists between biosynthesis of the amines and their enzymatic degradation. Any alteration in this balance can theoretically

*Department of Pharmacology, School of Medicine, University of Washington, Seattle, Washington.

1. Davison, A. N.: *Physiology. Rev.* 38:729,1958.
2. Sjoerdsma, A., et al.: *J. Pharmacol. Exp. Therap.* 126:217,1959.

alter brain function.

When a monoamine oxidase-inhibiting substance is introduced into the system, the balance is upset and levels of both free and depot amines are increased.[3]

An increase in brain levels of the amines, serotonin and/or norepinephrine, is believed to be chiefly responsible for the psychic stimulation associated with monoamine oxidase inhibitors. The belief is supported by the fact that central nervous system stimulation occurs when the amino acid precursors of serotonin and norepinephrine are administered to experimental animals to produce higher brain levels of the amines.[4]

The concept of MAO-inhibition as a source of central stimulation is not new. Some 20 years ago, it was suggested as an explanation of the central stimulatory effects of amphetamine.[5] However, *in vivo* inhibition of monoamine oxidase could not be demonstrated with doses of amphetamine capable of producing central stimulation.[6] Furthermore, the extremely rapid onset of amphetamine action is poorly compatible with enzyme inhibition as a mode of action.

On the other hand, inhibition of brain monoamine oxidase does appear to be the basic mode of action for the production of central stimulatory effects by such compounds as iproniazid, β-phenylisopropyl hydrazine (JB-516)*, and their analogues. These compounds produce an irreversible and prolonged inhibition of monoamine oxidase both *in vivo* and *in vitro*.[7] They differ, however, in certain important pharmacological respects which may alter their relative clinical efficacy considerably.

EXPERIMENTAL STUDIES

Comparison of the MAO-inhibitory action of iproniazid and JB-516 indicates the latter to be roughly 10 to 40 times more potent than iproniazid, both *in vitro* and *in vivo*.[2,8-11] MAO-inhibiting potency of the two compounds *in vitro* was determined by incubating rat liver and brain homogenates having known monoamine oxidase activity with serotonin; determining the amounts of serotonin remaining after appropriate time intervals; and then repeating the procedure with the addition of iproniazid or JB-516. In these studies, 10^{-6} molar concentration of JB-516 produced approximately the same degree of inhibition of monoamine oxidase as did $5x10^{-5}$ molar concentrations of iproniazid.[8]

Several indices of MAO-inhibition in laboratory animals have been employed, among them the potentiation of the pyretogenic effect of 5-hydroxytryptophan.[8,9] In doses of 50 mg. per kg. or more in rabbits, this compound produces hyperthermia similar to that observed with lysergic acid diethylamide.[11] It is presumed that the hyperthermia is due to the formation of serotonin by decarboxylation of 5-hydroxytryptophan since the rate of serotonin formation corresponds well with the onset of the pyretogenic effect.[12] In addition to ele-

*Catron®, Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

3. Spector, S., et al.: *Science*, 127:704,1958.
4. Bogdanski, D. F., et al.: *J. Pharmacol. Exp. Therap.*, 1222:182,1958.
5. Mann, P. J. G., & Quastel, J. H.: *Biochem. J.*, 34:414,1940.
6. Schayer, R. W.: *Proc. Soc. Exp. Biol. Med.*, 84: 60,1953.
7. Davison, A. N.: *Arch. Biochem. Biophys.*, 77: 368,1958.
8. Horita, A.: *J. Pharmacol. Exp. Therap.* 122:176, 1958.
9. Gogerty, J. H., & Horita, A.: *Fed. Proc.*, 18:395, 1959.
10. Tedeschi, D. H., et al.: *J. Pharmacol. Exp. Therap.* 126:225,1959.
11. Horita, A., & Gogerty, J. H.: *J. Exp. Pharmacol. Therapy.*, 122:195,1958.
12. Udenfriend, S., et al.: *J. Biol. Chem.*, 224:803, 1957.

vation of temperature, central nervous system excitation is also observed.[12] The administration of monoamine oxidase-inhibiting substances potentiates the pyretogenic effect of 5-hydroxytryptophan. In this respect, JB-516 is capable of potentiation at doses one-twentieth to one-fortieth that of iproniazid.[8,11] This marked potentiation of the pyretogenic effect of 5-hydroxytryptophan persists for an unusually long period of time. With a potentiating dose of 10 mg. of JB-516, rabbits given 20 mg. of 5-hydroxytryptophan exhibit sharp temperature elevation for at least 6 days, with some residual effect even on the ninth day after administration.[8] Prolonged duration of action of this sort suggests that JB-516 is tightly bound to the enzyme system and requires a considerable period of time for detachment or destruction.

A similar technique for evaluating MAO-inhibiting potency in laboratory animals involves the potentiation of the convulsant effects of tryptamine, presumably through blockage of the oxidative deamination of this amine. In a recent series of experiments, JB-516 was found to be approximately nine times more potent than iproniazid in this respect.[10]

In humans, the earlier method of measuring MAO-inhibiting potency required the oral administration of serotonin and the subsequent determination of the decrease in urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid, in response to MAO-inhibiting compounds. In this test, also, JB-516 exhibits considerably greater potency than does iproniazid.[13,14]

13. Sjoerdsma, A., et al., *Lancet*, 2:159,1958.
14. Sjoerdsma, A., et al., A method for measurement of monoamine oxidase inhibition in man and its clinical application, Conf. of Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. Nov. 20-22, 1958.

More recently, a technique of measuring urinary levels of tryptamine has been employed. Tryptamine is metabolized, primarily by monoamine oxidase, to indole-3-acetic acid; thus, direct measurement of the increased amounts of an enzyme substrate rather than decreases in the level of its metabolite is possible. Using this determination, it was found that a markedly greater increase in daily urinary tryptamine occurred with JB-516 at doses of 12.5 or 25 mg. per day than with iproniazid at a dosage of 50 mg. per day.[2]

In vivo studies indicate that JB-516, unlike iproniazid, possesses a marked selectivity for brain monoamine oxidase in preference to that of the liver. Progressively increasing doses of iproniazid inhibit liver MAO first. The brain enzyme is affected only at considerably higher dosages. In contrast, JB-516 produces significant inhibition of brain MAO at doses which have little or no effect on the MAO of the liver.[9]

This difference in organ selectivity appears to be related to the relative ability of JB-516, and inability of iproniazid, to cross the blood-brain barrier. Studies with two other structurally related compounds, 1-isonicotinyl-2-phenylisopropylhydrazine and isopropylhydrazine lend support to this hypothesis.[15] The isonicotinyl compound exhibits a typical iproniazid-like preference for liver MAO *in vivo*. Since it differs from JB-516 only in the presence of the isonicotinyl group, it is inferred that this chemical moiety hinders the passage of the molecule through the blood-brain barrier. An isonicotinyl group is also present in iproniazid, partially explaining its poor affinity for brain MAO *in vivo*. In addition, the iso-

15. Horita, A., et al.: *Fed. Proc.*, 81:403,1959.

propylhydrazine moiety of iproniazid, when tested alone, also demonstrated poor affinity for brain MAO *in vivo*.

The presence of the benzene ring is apparently of critical importance for passage across the blood-brain barrier. Substitution of various alkyl, alkoxy, or halide groups for the benzene ring in the JB-516 molecule led to decreased brain MAO selectivity. A similar loss of blood-brain permeability as well as loss of potency occurred when substitutions were made on the terminal hydrazine group of the molecule. Of the compounds tested, JB-516 (β-phenylisopropyl hydrazine) produced the most potent and selective inhibition of brain MAO. While phenylethylhydrazine was comparable in selectivity, it was less potent. Theoretically, this structure-activity relationship should have important clinical connotations, in that higher brain selectivity might be expected to minimize accumulation of the MAO inhibitor in the liver and other peripheral tissues. In this respect, JB-516 appears to possess the optimal chemical structure for maximum inhibition of brain MAO with minimal effects on other organ systems.

In 41 normal subjects, JB-516 was administered for prolonged periods to determine the effects of the drug on organs and systems other than brain monoamine oxidase.[16] Studies were made of glucose tolerance, liver function, renal tolerance, urinary bladder contractility, semen count, urinary steroid levels, thyroid function, serum electrophoretic patterns, and hematologic effects. While some flattening of the glucose tolerance curve occurred in 3 patients, other measures of metabolic function were within normal limits. The low toxicity of JB-516 at clinically effective dosage further confirms its optimal structure for inhibition of brain MAO with little action on peripheral organs.

SUMMARY

The studies described suggest that it is important to consider not only potency but also the ability of a given drug to cross the blood-brain barrier in predicting clinical usefulness of the compounds. Drugs possessing greater selectivity for the brain minimize the hazards of possible accumulation in the liver and other peripheral sites.

The optimal chemical structure of the arylalkyhydrazines for inhibition of brain monoamine oxidase *in vivo* consists of an unsubstituted benzene ring, an isopropyl side chain, and an unsubstituted terminal hydrazine group.◀

16. Agin, H. V., & Greenblatt, I. J.: Studies with amine oxidase inhibitors, Scientific Exhibit, 153rd Annual Convention, Medical Society of the State of New York, Buffalo, May 9-19, 1959.

Acute Poliomyelitis Therapy

Convalescents' serum, gamma globulin, and antibiotics all proved ineffective. An effective specific treatment is theoretically impossible. Laboratory studies in a history presented indicate that viremia and invasion of the central nervous system by the virus take place at a time when there is no suspicion of poliomyelitis. So, therapy would always come too late even if a specific therapy was available. Good nursing care is helpful. Paralysis of deglutition and respiration requires special measures, most effectively supplied in special poliomyelitis centers having special material and specially trained personnel.

Zischinsky, H., *Munchen. med. Wchnschr.*, 101:30-33,1959.

ORIGINAL ARTICLE

Monoamine Oxidase Inhibitors in the Treatment of Angina Pectoris

Over 70 per cent of 31 patients experienced notable relief while receiving isocarboxazid

GEORGE C. GRIFFITH, M.D., *Los Angeles, California*

The monoamine oxidase inhibitors, of which iproniazid is one, are potent agents in the therapy of angina pectoris, a disease which hitherto has been very discouraging to treat. Two important factors are operative in angina: the psychic component, and the factor of myocardial ischemia.

Iproniazid has proven effective in the treatment of many depressive states and in contributing to the patient's feeling of well-being; this is of great importance in the therapy of the patient with angina, who not only is limited in his capacity for effort but usually is fearful of the outcome of his illness. The patient with angina who receives iproniazid can walk distances which formerly were out of the question for him and go about his daily tasks, within limits, without experiencing anginal pain or even feelings of pressure. If the drug is stopped or reduced below the effective level for the individual patient, his capacity for effort becomes increasingly limited, and he is forced to return to his pretreatment inactivity.

Now the foremost question is whether—with pain no longer a limiting factor on physical exertion of patients who respond well to the monoamine oxidase inhibitors—these patients possibly may attempt too much for their physical welfare.

PERSONAL EXPERIENCES

My first-hand experience with iproniazid has been limited to its use in 14 patients, one of whom succumbed to myocardial infarction within a few days of the start of medication—before the drug had received a sufficient trial. In two patients severe hypotension developed, which necessitated discontinuance of the drug, in the first patient after only four weeks of therapy; the second died of uremia after seven weeks, during which time iproniazid afforded him no relief. One of the remaining 11 refused to continue treatment after the second week because he perceived no benefit. The ten patients who experienced benefit from iproniazid administration received between 50 and 150 mg. of the preparation daily for periods of four to 32 weeks, without significant complication save for slight euphoria in one patient. Anginal pain stopped completely in these patients seven to 14 days after the start of iproniazid.

MAY CAUSE ORTHOSTATIC HYPOTENSION

The cardinal drawback of iproniazid therapy, both in my experience and in other reports in the literature, has been the occurrence of orthostatic hypotension in a significant proportion of patients.[1-4] Peripheral neuritis has been reported in up to 20 per cent of patients on iproniazid.[5] Hepatic damage, too, has been reported as a severe complication.[6] Neither peripheral neuritis nor hepatic damage was noted in my patients.

DEVELOPMENT AND TRIAL OF ANALOGS

To overcome the deficiencies of iproniazid and other early monoamine oxidase inhibitors, several analogs of these preparations have been developed. The exact mechanism whereby these agents relieve angina is not well understood. *In vitro* studies and animal experiments with one of the newer iproniazid analogs, isocarboxazid,* chemically 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine, indicate that this compound potentiates the activity of biological amines, such as serotonin.

Thirty-one patients, 21 men and 10 women with myocardial ischemia, were treated with isocarboxazid for periods ranging from one to nine months. The patients' age range was from early forties into the seventies. All had angina pectoris. In some, the angina apparently was due to uncomplicated coronary atherosclerosis; in others, pre-existing myocardial infarction, hypertensive cardiovascular disease, aortic stenosis, or heart failure was responsible. About one-half were seriously ill. In this preliminary investigation, the patients were used as their own controls. We feel that this is acceptable in a pilot study such as this, as most of the patients had been under care for periods sufficiently long for us to know each one's usual response to changes in procedure and medication. Response to the medication was judged by severity of pain, average number of daily anginal attacks, and the number of nitroglycerin tablets used.

1. Cesarman, T., *J. Clin. & Exper. Psychopath.*, 19:169,(Supplement) 1958.
2. Master, A. M., *Am. Heart J.*, 56:560 1958.
3. Banghart, H., *J. Clin. & Exper. Psychopath.*, 19:114,(Supplement) 1958.
4. Cesarman, T., *J. Clin. & Exper. Psychopath.*, 19:158,(Supplement) 1958.
5. Scherbel, A. L., & Harrison, J. W., The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis. To be published.
6. Feld, M., The Use of Marsilid in an Acute Intensive Treatment Center. Report, Symposium on Marsilid and Other Monoamine Oxidase Inhibitors, San Francisco, September 26, 1958.

*Marsilan™, Roche Laboratories, Division Hoffmann-LaRoche Inc., Nutley 10, New Jersey.

METHOD OF ADMINISTRATION

Patients were started on small doses of the drug, usually 15 to 30 mg. daily in divided doses. At the outset, 15 mg. per day were given, and as patients demonstrated tolerance, this was rapidly increased. We rarely have gone above 30 mg. per day. In the majority maximum benefit has been achieved at that range. Several have been unable to tolerate more than 15 mg. per day. One has been able to increase to 20 mg. per day, by gradual increments of 5 mg. daily at monthly intervals. At more rapid rates of increase nausea and vomiting have developed.

RESULTS

In general, patients felt better under medication with the iproniazid analog than previously. They were more alert, more cheerful, and could do more than formerly. Over 70 per cent of the patients reported notable benefit from these preparations. I look upon the monoamine oxidase inhibitors as a most important advance in the treatment of patients with angina.◀

The Diagnosis of Brain Tumors

The classical triad—headache, vomiting and choked disc—brings tumor to mind at once, but these come late from increased intracranial pressure. Most such patients will have had earlier signs and symptoms and will have seen several doctors. An intracranial tumor usually causes progressive loss of neurological function. In many cases there is loss of olfactory sense on the side of the lesion with slight facial weakness on the opposite side. Olfactory groove meningioma also may produce ipsilateral primary optic atrophy and contralateral papilledema. A convulsive seizure which appears for the first time in an adult must be suspected of being due to a brain tumor.

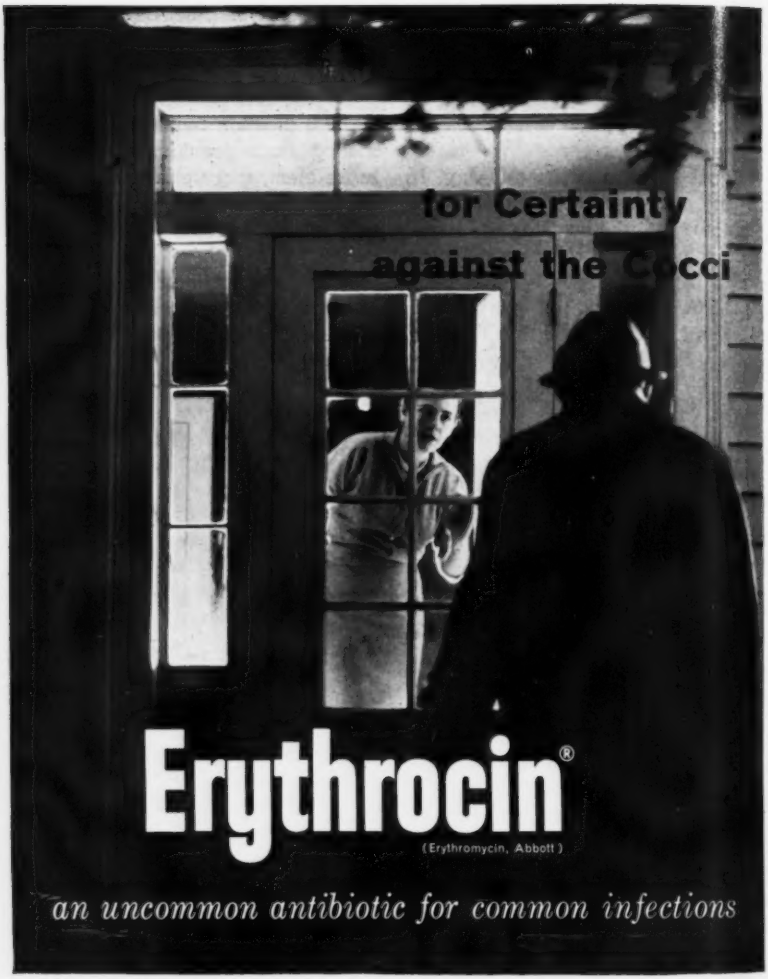
A tumor in the postcentral area often produces tingling, electric shocks, a feeling of insects on the skin, etc. There may also be loss of ability to locate a painful stimulus, measure its intensity and loss of stereognostic ability.

Aphasia results from a lesion in the left Broca's area in the right-handed person and vice versa. Tumors in the dominant superior temporal convolution may produce auditory seizures, or seizures with memory patterns. Occipital lobe irritative lesions produce hallucinations of lights or stars in the opposite visual field, or epileptic seizures ushered in by such aura. A paralytic or destructive lesion causes loss of central vision on the opposite side.

The chromophile adenomas produce acromegaly, the chromophobe adenomas produce the fat boy and the plump effeminate hypopituitary adult. Often the beginning symptoms are loss of vision in the temporal fields, polyuria, polydypsia and a hunger for sweets.

Lumbar puncture is hazardous in the presence of the signs of intracranial pressure. The role of the internist or general practitioner is to recognize that the patient's symptoms suggest intracranial tumor and to refer the patient to the specialist.

Gage, E. L., *West Virginia M.J.*, 55:147-154,1959.



Provides fast, high blood and tissue concentrations—plus an unparalleled safety record. Erythrocin is available in easy-to-swallow Filmtabs® (100 and 250 mg.); in tasty, citrus-flavored Oral Suspension (200 mg. per 5-cc. teaspoonful); and for intravenous and intramuscular use.

ABBOTT

®FILMTABS—FILM-SEALED TABLETS, ABBOTT, U.S. PAT. NO. 2,881,095

909132

ORIGINAL ARTICLE

Isocarboxazid: A New Antidepressant Drug

This medication produced good to excellent results in 25 of 28 patients with various depressional disorders

R. B. FORD, M.D., H. E. BRANHAM, M.D., and J. J. CLECKLEY, M.D., *Charleston, South Carolina*

The purpose of this study was to investigate by the double blind technique the antidepressant activity and possible side effects of a new iproniazid* analogue, isocarboxazid,† 1-benzyl-2-(5-methyl-3-isoxazolycarbonyl) hydrazine. This drug was reported to be 6 times as potent as iproniazid in inhibiting amino oxidase *in vitro* and 30 times as potent an inhibitor in the brain of rats *in vivo*. It was 8 times as strong as iproniazid in potentiating the central excitant action of 5-hydroxytryptophane in mice. This indicates that the compound potentiates the activity of biological amines such as serotonin. The drug was also 7 times as strong as iproniazid in blocking reserpine ptosis in mice. The acute toxicity *p.o.* for rats in terms of LD_{50} was found to be 470 mg./kg. as compared to 383 mg./kg. for iproniazid. For the mouse *i.p.* the figures were 110 mg./kg. for isocarboxazid, 690 mg./kg. for iproniazid. Symptoms noted in animals given toxic doses of isocarboxazid were increased aggressiveness and loss of weight, and death was by convulsions.[1]

From the Department of Psychiatry, Medical College of South Carolina.

*Marsilid®, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey.

†*Marplan™*, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey.

1. Department of Clinical Investigation, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey.

TABLE 1

RESPONSE TO ISOCARBOXAZID (DOUBLE BLIND STUDY)

Diagnosis	Number of Patients	Results of Therapy			
		Excellent	Good	Fair	Poor
Neurotic depressive reaction (acute & chronic)	4	3	1	0	0
Involutional depression agitated	6	4	2	0	0
Schizo-affective reaction, depressed	2	0	2	0	0

TABLE 2

RESPONSE TO ISOCARBOXAZID (NOT A DOUBLE BLIND STUDY)

Diagnosis	Number of Patients	Results of Therapy			
		Excellent	Good	Fair	Poor
Neurotic depression acute & chronic	8	4	3	1	0
Involutional depression agitated	5	1	2	1	1
Schizo-affective reaction, depressed	2	0	2	0	0
Manic-depressive reaction, depressed	1	1	0	0	0

This study includes two groups of patients. Members of the first group of 15 were studied by the double blind technique, members of the second group of 16 were given the active drug and their response evaluated. Most of those in the double blind study were chronically depressed clinic patients while most of the second group were private patients. Any patient with a depressive component to his illness was accepted for the study provided he had received no psychic energizer or EST for a period of 4 weeks prior to the beginning of the study, and had no history of liver disease. The patients were seen at weekly intervals and received no psychotherapy other than simple reassurance. Dosage of the drug ranged from 10 mg. daily to 30 mg. daily. Usually the starting dose was 20 mg., with reduction to 10 mg. after initial improvement was recorded. Temperature, weight, and blood pressure were noted at weekly intervals.

RESULTS

The patients were rated on the following points:

1. Degree of depression.
2. Psychomotor activity.
3. Disturbance of sleep pattern.
4. General interest.
5. Productivity.

In the double blind study group 13 patients received the active drug and 7 showed excellent results, 5 good results, and 1 failed to return for sufficient follow-up. A total of 9 patients received the placebo and 1 showed good response, 6 slight response, 1 no response, and 1 failed to return for sufficient follow-up. All patients included in this study had been followed for a minimum of 3 months.

TABLE 3

RESPONSE TO ISOCARBOXAZID (TABLES 1 AND 2 COMBINED)

Diagnosis	Number of Patients	Results of Therapy			
		Excellent	Good	Fair	Poor
Neurotic depression acute & chronic	12	7	4	1	0
Involutional depression agitated	11	5	4	1	1
Schizo-affective reaction, depressed	4	0	4	0	0
Manic depressive reaction, depressed	1	1	0	0	0
Total	28	13	12	2	1

most for 5 months. Response of the first group to isocarboxazid were 7 excellent, and 5 good. The response by diagnostic categories for the double blind study are shown in Table 1.

Response of the second study group (not double blind) to the drug were 6 excellent, 7 good, 2 fair and 1 poor. The response by diagnostic categories is shown in Table 2.

Combining the two groups (Table 3) the following results were obtained: 13 excellent, 12 good, 2 fair, and 1 poor.

SIDE REACTIONS

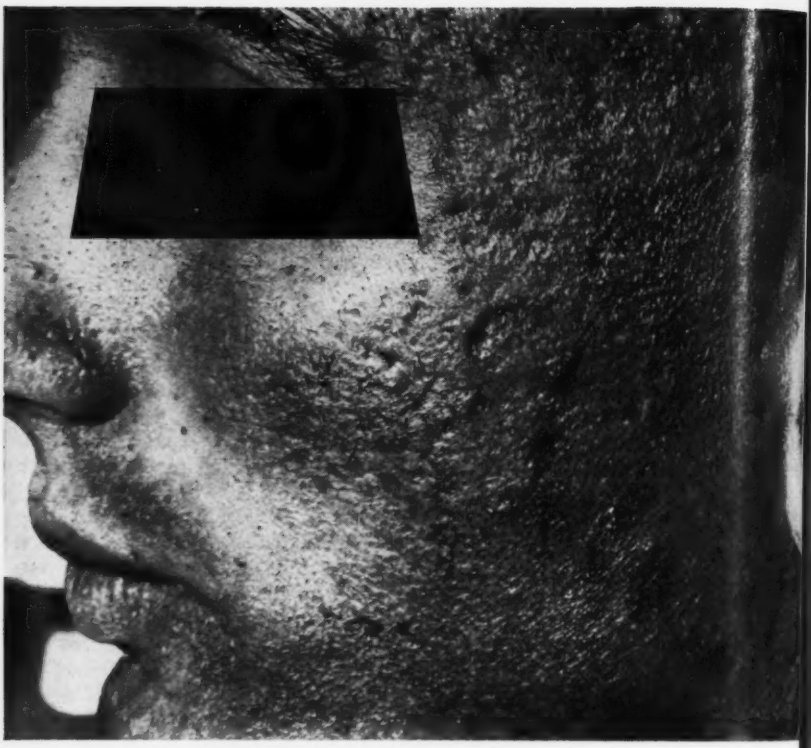
There were no serious side reactions noted except for moderate relative hypotension in 4 patients and only 2 of these reported symptoms. The greatest drop in blood pressure noted was from 160/110 to 130/90. One case of leukopenia, confirmed by bone marrow as granulocytic depression, was noted in a patient who had never received the active drug and was on the placebo at the time. This was coincident with an acute viral gastro-enteritis and was attributed to it. Frequent complete blood counts and urinalyses were normal except for the leukopenia noted above. Cephalin cholesterol flocculation tests obtained before, during, and at the completion of the series failed to show any evidence of liver damage.

DISCUSSION

In this small series of patients the drug usually produced good to excellent results at a smaller dosage level than is usually employed with iproniazid. Only in rare instances was 30 mg. daily required, and one patient showed akathisia which disappeared when the dosage was reduced to 20 mg. daily. Best results were obtained in reactive depressions and the one manic-depressive showed an excellent response. All 4 schizo-affectives showed almost complete relief of their depression but their thinking disturbances remained unchanged. The patient showing good response on placebo for only a 2-week period was then unknowingly switched to the active drug and continued to show improvement.

SUMMARY AND CONCLUSIONS

The results obtained from this study of 28 patients indicate that isocarboxazid is very useful in the treatment of depression and bears further investigation. There was a significant absence of toxic effects.◀



these physical scars need never have developed

If this man had sought early treatment, these scars might never have developed.

A physician's advice and guidance concerning his condition, plus treatment with 'Acnomel', might have prevented his acne from progressing to the severe, scarring stage.

'Acnomel' conceals acne lesions as it heals them, thus reducing embarrassment while treatment goes on. The results from 'Acnomel' therapy are often evident in a few days rather than in weeks or months.

When you see a patient who needs advice about acne, remember 'Acnomel'. Available in 2 forms: Cream for use at home; Cake in a handy compact for use away from home.

Acnomel* **conceals as it heals**

sulfur • resorcinol • hexachlorophene

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat.

ORIGINAL ARTICLE

Treatment of Angina Pectoris with Nialamide

Of 59 patients treated with the drug, 46 experienced 50 per cent or more relief from symptoms

JOSEPH B. WOLFFE, M.D.,* and HARRY SHUBIN, M.D.,*
Philadelphia, Pennsylvania

The central nervous system stimulating effect of the amine oxidase inhibitor, iproniazid (1-isonicotinyl-2-isopropyl hydrazine) was first observed as a side effect in the treatment of tuberculosis.[1-3] Subsequently this feature was recognized as beneficial in the treatment of depressed states[4] as well as in other conditions where depression often is a major contributory factor, including ulcerative colitis,[5] rheumatoid arthritis,[5,6] and angina pectoris.[7-15]

OF BENEFIT IN ANGINA

The salutary effect of iproniazid on angina pectoris was reported in 1957,

*From the Department of Medicine, Valley Forge Medical Center and Heart Hospital, Norristown, Pa., and the Wolffe Clinic and Hospital.

This study was supported in part by a grant from the Valley Forge Heart Research Foundation, and in part by a grant from Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

1. Selikoff, I. J., et al., *Quart. Bull. Sea View Hosp.*, 13:17-26,1952.
2. Coates, E. O., Jr., et al., *Arch. Int. Med.*, 93: 541-549,1954.
3. O'Connor, J. B., et al., *Am. Rev. Tuberc.*, 68: 270-272,1953.
4. Kline, N. S., *J. Clin. & Exper. Psychopath.*, 19 (Supp.1):72-79,1958.
5. Banghart, H. E., Marsilid Symposium, New York, November, 1957.
6. Scherbel, A. L., *Cleveland Clin. Quart.*, 24:90-97,1957.
7. Cesarman, T., *Arch. Inst. Cardiol., Mexico.*, 27: 563-580,1957.
8. Cossio, P., *Presna Med. Argent.*, 44:2679-2693, 1957.
9. Cesarman, T., *J. Clin. & Exper. Psychopath.*, 19 (Supp.1):169-177,1958.
10. Cossio, P., *Am. Heart J.*, 56:113-118,1958.
11. Masters, A. M., *Am. Heart J.*, 56:570-582,1958.
12. Towers, M. K., Wood, P., *Brit. M.J.*, 1067-1068,1958.
13. Masters, A. M., & Donoso, E., Conference on amine oxidase inhibitors. New York Academy of Sciences, New York, Nov. 20-22,1958.
14. Cossio, P., Contribution of Iproniazid to the Treatment of Angina Pectoris, Ibid.
15. Schweizer, W., Isopropylhydrazides in Angina Pectoris. Ibid.

and subsequently confirmed in various clinics[7-16] Improvement has been manifested by more freedom from pain, decreased nitrite requirements, and relief from fear and anxiety. Improvement as measured by exercise tolerance and correction of ECG abnormalities has been claimed,[12,15] but not confirmed.[11,13] ECG deterioration consistent with coronary insufficiency has been observed during therapy although the patient remained pain-free.[11,12]

ORTHOSTATIC HYPOTENSION

It is reasonable to assign some of the reported instances of coronary insufficiency to the often profound drop in arterial blood pressure resulting from this medication. The loss of pain perception and occasional euphoria, leading the patient to engage in undue physical activity, have also been incriminated. However, it is difficult to differentiate some of the effects attributed to iproniazid from events in the natural history of the disease.

Animal studies of the effects of iproniazid on coronary circulation suggest significant enhancement of the coronary blood flow. A 65% increase in the ratio of the coronary blood flow to left ventricular activity has been reported.[17] A significantly increased survival rate has been demonstrated in dogs subjected to acute coronary occlusion when pretreated with iproniazid.[18] Such animal data is of interest but its significance in relation to the clinical syndrome of angina pectoris is questionable.

The usefulness of iproniazid in angina as well as most other conditions has been seriously limited by its toxicity, particularly orthostatic hypotension and hepatitis, the latter occasionally fatal. Nialamide* (N-isonicotinyl-N[1]-(beta-N-benzyl-carboamido-ethyl)-hydrazine is a recently synthesized, potent monoamine oxidase inhibitor. It is of particular interest because significant orthostatic hypotension has not been observed in clinical trials. There have been no reports of hepatic or hematologic disturbances.[19] Nialamide's value as a potent psychic energizer was demonstrated in preliminary studies.[19] These features of the drug encouraged us to evaluate its efficacy in the treatment of angina pectoris.

SELECTION OF PATIENTS AND METHODS

The 59 patients selected for this study had typical anginal syndrome of moderate or greater severity and, except for temporary relief of acute attacks by nitroglycerin, a history of poor response to conventional antianginal agents. Several had been subjected to surgical procedures for the relief of angina or had received therapeutic amounts of radioactive iodine, without benefit. All had had their anginal problem for more than one year; all were known to the investigators for at least one year—circumstances tending to assure little likelihood of spontaneous remission.

The patients were followed closely in the laboratory as well as clinically. Prior to, and periodically during the course of study, the examinations made were: ECGs, complete blood counts, urinalyses, blood urea nitrogens, serum cholesterols, and all usu-

16. Grauman, S. J., *Am. J. Cardiol.*, 3:544-546,1959.
17. Crumpton, C. W., Castillo, C. A., Rowe, G. G., & Maxwell, G. M., Serotonin and the Dynamics of the Heart—Conference on Amine-oxidase Inhibitors, New York Academy of Sciences, N.Y. Nov. 20-22, 1958.
18. Regelson, W., Hoffmeister, F. S., & Rubin, H., Effect of Iproniazid on Survival Following Acute Coronary Occlusion In the Dog—Conference on Amine-oxidase Inhibitors, New York Academy of Sciences, N. Y., November 20-22, 1958.
19. Conference on Nialamide: A New Psychotherapeutic Agent, Conducted by Eastern Psychiatric Research Association, June 6, 1959.

*Niamid®, Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

al liver-function tests (transaminase, alkaline phosphatase, thymol turbidity, cephalin flocculation, direct and indirect bilirubins, and icteric index).

Dosage of nialamide was on the conservative side, particularly initially—usually started on 12.5 mg. t.i.d., this dose revised upward, depending upon responses, with weekly increments of 12.5 mg. per dose. Most patients had 25 mg. t.i.d., a few as much as 50 mg. t.i.d.

RESULTS OF STUDY

Therapeutic results with nialamide in the form of symptomatic relief have been striking not only in numbers of patients improved, but also in the degree of benefit seen in many cases. Brief histories of some representative cases are as follows:

Case Histories

1. White woman aged 66 years. Diagnosis: Atherosclerotic cardiovascular disease, angina pectoris secondary to coronary insufficiency, status anginosus.

Patient first complained of angina of effort in 1954. She received the usual antianginal drugs. Symptomatic relief could only be obtained with intravenous administration of ouabain and aminophylline. Beneficial effect from each injection lasted for 3 days. Patient was able to follow gainful occupation until March, 1959, when status anginosus developed; 12.5 mg. nialamide b.i.d., gave some relief but patient complained of nausea, dizziness and coldness of lower extremities. These side effects subsided, and patient later tolerated 25 mg. nialamide t.i.d. Improvement was gradual at inception of therapy. Nialamide was then replaced by another analogue of iproniazid, which caused almost immediate recurrence of status anginosus, accompanied by severe nausea, weakness and dizziness. The analogue was discontinued and nialamide reinstituted. Relief was almost immediate and has continued to a point where patient is considering return to part-time employment.

2. White man aged 65 years. Diagnosis: Atherosclerotic cardiovascular disease, myocardial disease secondary to coronary insufficiency, left ventricular aneurysm, effort angina and angina decubitus.

Patient first experienced chest pain typical of angina pectoris, relieved by nitroglycerine, 17 years ago. Two years later he experienced his first coronary thrombosis, with subsequent complete freedom from anginal attacks. Relief lasted for one year, after which angina pectoris recurred which was partly relieved by conventional antianginal therapy. Anginal attacks continued until he suffered a second coronary thrombosis with myocardial infarction, 3 years after the first. Again the anginal attacks subsided for two years, when a 3rd occlusive episode occurred. The anginal attacks persisted and responded only to intravenous injections of ouabain combined with aminophylline. Deterioration continued, objectively and subjectively. Left ventricular aneurysm was seen on x-ray picture and the ECG showed progressive myocardial changes. Finally he developed angina decubitus. The severity of the anginal syndrome gave rise to an anxiety state and depression, alternating with periods of agitation. The anginal syndrome had become refractory to therapy including I^{131}. In January, 1959, the patient was given nialamide 25 mg. b.i.d., which gave relief in 3 days, definite improvement of the anxiety state and a better mental outlook. Anginal pain was substantially reduced. When he experienced an anginal attack the pain was so slight and fleeting that nitroglycerin has become unnecessary for the past 3 months.

3. White man, aged 51 years. Diagnosis: Atherosclerotic cardiovascular disease, myocardial disease secondary to coronary insufficiency, effort angina.

First attack of angina pectoris in October, 1956. Acute coronary thrombosis in December, 1956, was followed by disappearance of angina pectoris. Anginal syndrome recurred early in 1958, and progressed in frequency and severity until July 1958, when he developed angina decubitus. The syndrome failed to respond to usual antianginal therapy. In October 1958 he developed status anginosus. Pericardial poudrage with talcum and application of 5% trichloracetic acid to the coronary vessels and the epicardium was successfully performed in October, 1958. Some temporary relief of the anginal syndrome resulted. Anginal attacks became gradually more frequent and severe until February, 1959, when nialamide 25 mg.

SUMMARY OF RESULTS OF STUDY IN 59 PATIENTS

Degree of Improvement	Number of Patients
Complete symptomatic relief	20
Symptomatic improvement (more than 50%)	26
Symptomatic improvement (less than 50%)	6
Unimproved	5
No follow-up	2

b.i.d. was given with satisfactory results. No side effects were noted. He was able to increase his activities and return to work. On May 9th at 4:00 A.M., while in bed, he suffered a crushing pain in the chest, and was re-admitted to the hospital with an acute coronary thrombosis.

4. White man, aged 44 years. Diagnosis: Atherosclerotic cardiovascular disease, myocardial infarction, angina pectoris.

First attack of angina pectoris in 1950 was treated for acute coronary insufficiency. Angina persisted and worsened until 1956, when he suffered an acute coronary thrombosis, following which the angina subsided for two months. Upon recurrence of anginal complaints he was given I^{131} without relief. Ligation of the internal mammary arteries was performed in April, 1957. For six weeks, he was mostly at rest. Then the anginal syndrome of increased severity and frequency prevented the following of gainful employment. Nialamide, 25 mg. t.i.d., started in January, 1959, afforded marked relief. The patient continues with therapy and has returned to gainful employment.

5. White man, aged 67 years. Diagnosis: Atherosclerotic cardiovascular disease, myocardial infarction, angina pectoris, myxedema due to I^{131} therapy, status anginosus.

First attack of angina pectoris in 1944. Angina persisted until he suffered acute coronary thrombosis in 1945, then subsided to recur at end of 1946, when he experienced a second coronary occlusion. Asymptomatic for six months, effort anginal attacks recurred, refractory to usual therapy. I^{131} was given in May, 1953, with resulting myxedema and some relief of anginal syndrome. Myxedema was rather troublesome. Thyroid 1/4 gr. could not be tolerated because of severe anginal attacks. Gradually anginal syndrome recurred and was relieved only by intravenous administration of ouabain combined with aminophylline. Status anginosus developed in April, 1959. Nialamide, 12.5 mg. t.i.d. gave marked relief and increased tolerance for thyroid. No side effects were noted. Patient continues on therapy.

6. White man, aged 64 years. Diagnosis: Rheumatic heart disease, aortic stenosis and insufficiency, mitral stenosis and insufficiency, cor bovinum, angina pectoris.

Patient was asymptomatic and worked as school janitor until one year ago, when he had typical attacks of angina pectoris. The usual drugs were ineffective. In March, 1959, nialamide, 24 mg. t.i.d., afforded relief. Patient continues therapy with good tolerance for effort.

SUMMARY OF CASES

Twenty-six of these patients had intractable angina or status anginosus; 18 of these made significant improvement; five had complete relief—symptoms recurred during a subsequent trial without nialamide, and subsided again upon reinstitution of the drug. Thirteen of the patients with intractable angina or status anginosus had relief greater than 50% and, in addition, a mood elevation in these previously depressed and discouraged individuals.

The earliest beneficial response was noted after two days of therapy. Some cases required continuous administration for as long as three weeks before any response was noted. As a rule the onset and development of symptomatic effect were gradual.

Nialamide was voluntarily discontinued by several patients. Anginal symptoms recurred as early as one day after interruption of drug in one patient, but did not recur for as long as one to four weeks in other cases.

Neither improvement nor deterioration of ECG findings attributable to the drug was noted. Two of these patients showed clinical and ECG changes consistent with acute coronary thrombosis, one three weeks and one four months after nialamide therapy. Neither had drug-induced hypotension. Symptomatic relief had been less than 50% in both cases.

No clinical or laboratory abnormalities of hepatic, renal, or hemopoietic systems attributable to the drug were observed.

Side effects from nialamide administration were noted in seven patients. Three of these complained of nausea, vertigo, and a feeling of coldness; these symptoms subsided within several days without discontinuation of therapy. A decrease in blood pressure was noted on only one occasion in only one patient—an asymptomatic 20 mm. fall in pressure from 180/92 to 160/80. Two patients became so euphoric as to require reduction in dosage. Two patients on the 50 mg., t.i.d. dosage complained of nervousness and insomnia; in these instances the drug was discontinued for three days, then resumed at 25 mg. t.i.d., with good tolerance and satisfactory results.

Three patients became aware of intermittent claudication while on nialamide therapy. It seems improbable that this was a direct effect of the drug. Alleviation of the anginal symptoms in these previously restricted persons enabled them to walk, thereby making evident their latent peripheral circulatory insufficiency.

Interesting incidental observations were made in eight patients with hypothyroidism—in one case due to an old thyroiditis and in seven to myxedema following I^{131} therapy. These patients were extremely uncomfortable because of their hypothyroid state of coldness, stiffness of the joints and upper lip, skin changes and weakness. However, thyroid administration, even in doses of ⅛-¼ grain, produced severe anginal pain. Then trials of nialamide in conjunction with thyroid were made. In patients on nialamide, small doses of thyroid, gradually increased, relieved hypothyroid symptoms without inducing severe angina. It was not possible to administer sufficient thyroid to completely eliminate the myxedema without producing recurrence of anginal attacks despite the use of nialamide.

DISCUSSION

There is no evidence of any effect on underlying organic pathology in patients with angina pectoris treated with nialamide. Hypoxia is not the only factor in bringing on the pain of angina pectoris. Tetany of the heart muscle has been advanced as a possible cause, but this seems unlikely since the heart continues to contract regularly during anginal attacks. Coronary vascular spasm as the cause seems highly improbable when judged by post mortem findings of many coronary vessels so sclerosed and rigid as to make a contraction impossible. Increased blood pressure during anginal attacks is not a consistent finding.

The highly sensitive person may have agonizing angina attacks in the presence of minor pathological

changes; while one less sensitive may have extensive interference with coronary circulation and yet be free from angina pectoris. We believe that one of the important factors of pain in angina pectoris is an abnormal reflex arc involving the adventitia of the coronary arteries through the coronary nerve plexuses.

Further, it is possible that the amine oxidase inhibitors, as typified by nialamide, relieve by peripheral interruption of an abnormal reflex arc, and/or a central suppression of the patient's highly receptive nervous system. The abnormal reactions caused by various stimuli, e.g., sex relations, and competitions of every-day-life, seem to be minimized by nialamide; minor irritations, and even major stresses, induce no more than slight anginal attacks. It is best to warn the patient against over-exertion and to stay within pretreatment capacity for exertion. This seems safest until we know more about the action of nialamide.

SUMMARY

Extensive clinical and laboratory evaluations have revealed no evidence of liver, kidney or hematopoietic toxicity of nialamide. This is in contrast to other monoamine oxidase inhibitors.

Nialamide does not seem to influence the underlying pathology and is most effective in patients with highly receptive nervous systems.

In our experience, nialamide has proven most valuable in the symptomatic relief of angina pectoris, as shown by 50% or more improvement in 46 of 59 patients.◀

ORIGINAL ARTICLE

The Treatment of Everyday Depressive Patients with Nialamide

Therapeutic effect is sometimes noted within three days, and optimal effect within three to four months

FRANK J. AYD, JR., M.D.,* *Baltimore, Maryland*

Most practicing physicians daily see patients whose symptoms are directly attributable to or are complicated by a depression. Such patients complain solely of melancholia; others deny feeling despondent, expressing, instead, what superficially appear to be anxiety or psychosomatic symptoms. In either case their symptoms may be the manifestation of a manic-depressive reaction, an involutional melancholia, an incipient schizophrenic illness, or a depression occurring in the course of a neurosis or personality disturbance. Irrespective of the basic psychiatric ailment, depression is, at the moment, the prime cause of the patient's disability and the major therapeutic target.

Depressive reactions are (1) endogenous, having a physiologic basis, and (2) reactive, abruptly following a psychologic stress. The former can further be separated into the retarded and agitated varieties. Although they may occur at any time of life, endogenous depressions are most common after age 35 in persons whose basic personality is cyclothymic (up-and-down) or obsessive.

The obsessives are readily detected by their demeanor in the doctor's of-

*Chief of Psychiatry, Franklin Square Hospital, Baltimore, Maryland.

fice. They are perfectionistic, meticulous, sensitive, passive, indecisive, anxious and torn between maintaining their self-imposed standards and the demands of living. They are easily upset when things are not in order. When depressed they are unable to conceal their anxiety over their inability to do things in their usual thorough manner.

A depression is manifested by symptoms of three kinds—physical, emotional and mental, occurring in varying degrees of intensity. They must be elicited by interrogation because the patient seldom mentions all of them. Typically, they evolve slowly over several months and, although all three sets occur simultaneously, the physical and emotional predominate in the early stages of depression. Thus, the patient reports that he has been harassed by fatigue which is most pronounced in the morning, interest in his usual activities has declined and anxiety mounted because his energy output fails to meet his psychologic needs and demands. Subsequently, the patient notes that he is apprehensive about himself, that he is less self-assured and self-confident, more sensitive to emotional and physical stimuli, and that his basic biologic functions are not up to par—his appetite is diminishing, he is losing weight, he sleeps less, awakens earlier and can't get back to sleep, and his sexual urge is waning. There is an upsurge in sympathetic-adrenal activity giving rise to headaches, light-headness, flushing of the face, sweating, particularly of the hands and feet, dryness of the mouth, palpitations, constrictions of the chest, gastric tension, urinary frequency, and diarrhea or constipation.

The emotional and mental manifestations of a depression help to distinguish it from an anxiety state or a psychosomatic illness. The depressed person may emphasize his anxiety but betrays his melancholic mood by a desire to cry or by crying spells, by egocentric obsessions and phobias, by self-derogation and by feelings of inadequacy. As he gives his history he may refer to himself as a failure, remarking: "I can't concentrate. My mind is a blank. I have no interest in anything. I don't want to go anywhere, see anybody or do anything. Everything, however little, is too much. I'm always afraid." These indications of psychomotor retardation are accompanied by expressions of guilt, obsessive concern with ailments such as cancer or heart disease, fears of losing sanity, and an intense desire for relief from his subjective distress.

The inertia and lassitude of a retarded depression may be replaced by agitation and psychomotor restlessness, the distinguishing features of an agitated depression. When this happens, the patient paces the floor, wrings his hands, and continually bemoans his fate. In addition to early morning awakening, the agitated depressive has trouble getting to sleep and seldom gets more than six hours of fitful sleep, even when medicated with sedatives and hypnotics. Because of his tortured self-concern and his relentless agitation the patient becomes preoccupied with thoughts of self-destruction as the only solution to his dilemma.

The ambulatory depressive is a therapeutic problem for a doctor. This is especially true of mild and moderately depressed patients. Treating them with barbiturates, tranquilizers and amphetamines generally has

been far from satisfactory. To wait for a spontaneous remission invites the risk of suicide, yet they do not appear ill enough to warrant referral to a psychiatrist or hospitalization. On the other hand the depression will not respond to the "pull yourself together" advice so often given.

The advent of antidepressant drugs gave new hope for the depressed patient and the solution of a knotty problem for the physician. The first of these drugs, although therapeutically effective, caused adverse side effects which limited its prescription for office patients. Consequently, general practitioners and specialists other than psychiatrists still have need for a chemical remedy effective and reasonably safe for their ambulatory depressed patients.

Nialamide* is a new antidepressant. It is a potent amine oxidase inhibitor which, unlike its predecessors, is relatively free of major side effects and thus has broad therapeutic application. The drug is neither a stimulant nor a euphoriant, but it cannot be prescribed indiscriminately without increasing the hazard of suicide. The physician who learns the art of nialamide therapy has at his disposal an effective means of treating depression.

The following comments are based on the experience of myself and my associates in treating 150 patients with nialamide during the past 6 months. These patients were all ambulatory and the majority of them had been seen first by their family physician or a non-psychiatric specialist. They were selected for nialamide therapy because depressed mood, psychomotor retardation, loss of interest, feelings of guilt, insomnia, anorexia and functional somatic symptoms were their predominant complaints.

Preliminary trials of nialamide in all types of depression have shown that the most effective initial daily dosage range is 75 to 150 mg.[1] This starting dose should be prescribed for 1 to 2 weeks; then, if there has been no benefit, the dosage should be increased at weekly intervals by increments of 25 mg. daily, until improvement occurs or the total dosage reaches 200 mg. a day. An exceptional patient will require still larger doses, but this should not be tried until the patient has been on 200 mg. daily for at least 6 weeks. There are two reasons for this precaution: nialamide, like all antidepressants, is slow in taking effect; and, the larger the dose, the greater the likelihood of side effects.

How long will it be before patients will begin to feel better? Experience has demonstrated that patients responsive to this drug may begin to improve within three days to two weeks, although most of them require three to four weeks of therapy before genuine clinical benefit is shown. This improvement is always noticeable first to the physician and relatives, and last to the patient. Within a month to six weeks the patient should be feeling better.

The therapeutic dose of nialamide for the individual patient should be maintained for one month after maximum therapeutic benefit has been obtained, thereafter gradually lowered over a three-month period. Depressive symptoms may recur as nialamide is withdrawn; however, immediate reinstitution of the previous therapeutic dose usually suffices to abolish them. As has been the case

*Niamid®, Chas. Pfizer & Co., Inc., Brooklyn, N.Y.

1. Conferenc on Nialamide: A New Psychotherapeutic Agent, Conducted by Eastern Psychiatric Research Association, June 6, 1959.

with tranquilizers, there are depressed patients who appear to need nialamide for an indefinite period to remain symptom-free.

Nialamide alone is usually sufficient for retarded depressives, even those with anxiety. In the latter, anxiety is merely secondary to the primary mood disturbance and this symptom remits as the depression is relieved by nialamide. However, since nialamide does not mitigate agitation or severe insomnia, this drug alone should not be prescribed for agitated depressives. Instead it should be combined with tranquilizers, sedatives and hypnotics. Nialamide has been administered conjointly with barbiturates and tranquilizers such as Thorazine, Vesprin, Compazine, Dartal, Trilafon, and Stelazine, without potentiation of the central depressant effects of these drugs, and without any adverse synergistic action.

Therapeutic doses of nialamide have caused minor reactions such as headaches, dryness of the mouth, sweating, hypotension, epigastric distress and edema of the ankles, most of them mild, with doses in excess of 100 mg. daily, and disappearing when the dose was lowered. It has not been necessary to stop nialamide because of side effects. Nialamide has not been responsible for delayed micturition, impotence, weakness and fatigue, muscle tremors, increased psychomotor activity or insomnia.[2] Hence, nialamide is unlikely to cause disability or undue discomfort. Its failure to produce postural hypotension enhances its safety for ambulatory patients.

COMMENT

The successful treatment of everyday depressive reactions with nialamide is contingent upon the judicious selection of patients and a comprehensive knowledge of this remedy. Since nialamide is a new drug, much remains to be learned about this potent amine oxidase inhibitor, especially as to possible side reactions. The toxicity of other amine oxidase inhibitors did not become known until they had been used widely. Hence, physicians prescribing nialamide should be vigilant to detect promptly such effects which may be distressing, disabling, or even fatal. Risk can be minimized by prescribing the lowest effective dose and by close supervision of the patient during the early treatment period. Fortunately, the known risks of nialamide are few compared to its therapeutic effectiveness and the potential seriousness of an untreated depression. Thus, it is a valuable drug for use by general practitioners and specialists, other than psychiatrists, for the office treatment of depressed patients.◀

2. Ayd, F. J., Jr., Bianco, E., & Zullo, L., Treatment of Depressive States in Ambulatory Patients, *Dis. Nerv. System, (Supplement)*, 20:34,1959.

ORIGINAL ARTICLE

Phenelzine: A Therapeutic Agent for Mental Depression

Endogenous depressions responded best to the drug, 85 per cent of 580 patients with this diagnosis showing good results

L. EARLE ARNOW, M.D., Ph.D., *Morris Plains, N. J.*

When reserpine is injected into laboratory animals in appropriate doses, profound depression (decreased responsiveness to stimuli, lack of motion, apathy) results. Reserpine is believed to react on cells in the brain in such a way that they lose their ability to conserve the amines, serotonin and norepinephrine.[1] As a result, these amines are continually manufactured and lost by brain cells long after all reserpine has disappeared. Serotonin is postulated to act as a chemical mediator for synapses that transmit impulses causing a net depressive response (apathy, decreased response to stimuli, lowered emotional tone). Norepinephrine, on the other hand, is postulated to mediate impulses resulting in mental stimulation (alertness, increased responsiveness to stimuli, increased emotional tone).

The biologic effect produced by reserpine can be explained by assuming that, although both these amines are secreted by the nerve cells, the balance between the rate of production and the rate of destruction of the two compounds is such that the observed effects are those attributed to serotonin.[1]

1. Brodie, B. B., & Shore, P. A., in Kline, N. S. (ed.) *Psychopharmacology Frontiers*, Little, Brown & Company, Boston, 1959, p. 413.

MONOAMINE OXIDASE

An important mechanism for the destruction of serotonin and norepinephrine in the body involves catalytic oxidation by an enzyme known as monoamine oxidase. Iproniazid (a drug introduced as a therapeutic agent against tuberculosis) was reported to inhibit the enzyme, both *in vitro* and *in vivo*.[2]

When iproniazid was given to experimental animals several hours prior to the administration of reserpine, the usual depression was not observed. Instead, the animals exhibited increased activity and alertness. It seemed that, in the absence of the major destructive enzyme, the net biologic effect was that caused by norepinephrine.[3,4]

Clinicial trials of iproniazid, with and without reserpine, were carried out, using psychotic patients.[5] Iproniazid was found to be effective against some types of mental depression. The administration of reserpine proved to be unnecessary.

THE SEARCH FOR A NEW COMPOUND

The screening procedure involved the injection of various compounds into mice in order to observe their effect on the accumulation of serotonin in the brain. Active compounds caused an increase.[6] (The level of norepinephrine increased also, but serotonin was chosen for analysis because it is a more specific substrate for monoamine oxidase). After many compounds had been tested in this way, β-phenylethylhydrazine, since named phenelzine,* was chosen for extensive biologic and clinical evaluation.

BIOCHEMICAL AND BIOLOGIC STUDIES

Both phenelzine and iproniazid were found to be powerful inhibitors of monoamine oxidase *in vitro*. The dose of phenelzine required to cause an increase of 50 per cent in the content of serotonin in the brains of mice proved to be 11 mg. per kg. The comparable dose of iproniazid was 90 mg. per kg. Phenelzine acted with great rapidity: appreciable increase in serotonin content occurred within 15 minutes after administration, and an increase of 50 per cent was reached in 45 minutes. In the case of iproniazid, six hours were required to attain an increase of 50 per cent. The effects of a single injection of drug were long lasting—the average level of serotonin in the brains of experimental animals did not return to normal for about 2 weeks. Monoamine oxidase activity became 50 per cent of normal in about 3 weeks.

Phenelzine appears to be absorbed completely when it is given by mouth. For example, the dose required to kill 50 per cent of a group of mice was found to be 90 mg. per kg. orally and 91 mg. per kg. intravenously.

RECENT BIOCHEMICAL STUDIES

Phenelzine appears to influence the level of serotonin in the brain, not only by inhibition of monoamine oxidase, but also by a different mechanism.[7] A dose of phenelzine that resulted in apparently complete inhibition of monoamine oxidase activity caused a rise in serotonin content from 0.7 mcg. per gm. of brain t

2. Zeller, E. A., & Barsky, J., *Proc. Soc. Exper. Biol. Med.*, 81:459,1952.
3. Chessin, M., et al., *Fed. Proc.*, 15:409,1956.
4. Brodie, B. B., et al., *J. Pharmacol. & Exper. Therap.*, 116:9,1956.
5. Loomer, H. P., et al., *Congressional Record*, 1957, pp. 1382-1390.
6. Chessin, M., et al., *Ann. New York Acad. Sc.*, In press.

*Nardil®, Warner-Chilcott Laboratories, Morris Plains, N. J.
7. Dubnick, B., et al., *personal communication.*

1.2 mcg. per gm. Injection of 4 times this dose unexpectedly caused a rise from the control level to 1.6 mcg. per gm. The level had fallen to 1.2 mcg. per gm. 24 hours later. A second injection of phenelzine caused a rise to 2 mcg. per gm. in spite of the fact that monoamine oxidase activity still was inhibited at least 95 per cent.

TOXICITY STUDIES

The signs of acute toxicity in mice were hyperexcitability, elevation of the tail (a reaction typically caused by powerful analgesics such as morphine), piloerection, salivation, lacrimation, convulsions, and death within 24 hours. Chronic toxicity studies of six months duration, using rats and dogs, were conducted. Careful tests of liver and kidney function in dogs, done at the beginning, middle, and end of the study, did not show any abnormalities of these organs. Gross and histologic studies of representative tissues at the conclusion of the test did not reveal significant pathologic changes. No untoward effects were observed in the rats, except that there was retardation of growth at high dosages (15 and 50 mg. per kg. daily).

CLINICAL MATERIAL

The clinical information in this report is from an analysis of 580 case records reported by 16 investigators.

CLASSIFICATION OF MENTAL DEPRESSIONS

The following classification proved to be useful in analyzing the clinical results obtained by different investigators:

1. Exogenous Depression: This type of depression originates *outside* of the patient (e.g., death in the family, business failure). Ordinarily this type of depression is self limited and frequently does not require therapy.

2. Endogenous Depression: This is a mental depression that does not have an obvious cause, although the patient may give a spurious explanation for it. It orginates *within* the patient. Two types of endogenous depression have been described: *overt* and *larval*.[8]

Overt depressions easily are diagnosed, since the patient is obviously sad and has feelings of hopelessness.

Larval depressions, on the other hand, are not so obvious, since manifestations of grief, sadness, and hopelessness are not expressed directly. These patients often complain of irritability ("I'm so nervous"), and may be given sedatives as a result of the failure of the physician to recognize the underlying depression. Another important complaint is dysphoria ("I'm just not interested in things or people any more."). If the physician asks, "What gives you most pleasure?", the usual answer is "Nothing." These patients also exhibit insomnia, poor appetite, poor judgment, poor concentration, and poor capacity for sustained effort. Often, the patient complains of dryness of the mouth, skin, and stools. Usually the symptoms are most marked in the morning.

The depressed phase of an affective (manic-depressive) psychosis really is an endogenous depression, but this group has been separated in making the present analysis.

It is particularly important to recognize and treat patients with endogenous depressions, since many of them are potential suicides.

8. Sainz, A., et al., *Psychiatric Quart.*, 32:273,1958.

THERAPEUTIC RESULTS

Phenelzine has proved to be most useful in the therapy of endogenous depressions. Of the patients with this diagnosis, 85 per cent obtained a good result, and 66 per cent of them had remissions. Clinical improvement usually was noted within a few days and optimal effects occurred within 1 to 3 weeks in most cases. The drug did not act as a mental stimulant; it simply removed the mental depression, thus restoring the patient to his former normal mental state. Several investigators have reported that the use of electroconvulsive therapy (ECT) at their institutions has been reduced by 80 to 100 per cent since this new type of drug became available.

The response of patients in the depressed phase of an affective psychosis has been good so far as the depression itself was concerned; 79 per cent of the patients had a good result, although the underlying psychosis was not cured.

Patients with schizophrenia showed little improvement although in some cases the drug eliminated depression.

Approximately half of a group of patients with various neuroses had good results.

OTHER RESULTS

In the course of studying the biologic activity of phenelzine, it was noted that the compound had analgetic activity in animals.[9] This property may account for occasional reports that the drug has been useful in relieving the pain of rheumatoid arthritis, osteoarthritis, and terminal cancer. It has been reported that phenelzine markedly reduced the frequency and severity of migraine.[10] Several investigators report that the drug seems to be effective in decreasing the number of attacks of angina pectoris. Several experiments have shown that phenelzine, given intravenously or intraduodenally to anesthetized dogs, is effective in increasing markedly coronary blood flow with only minimal elevation of femoral arterial pressure.[11]

9. Emele, J. F., et al., *Fed. Proc.*, 18:387,1959.

SIDE EFFECTS

Side effects have been minor; no report indicates positive laboratory or clinical evidence of organ damage or of blood dyscrasias.

The incidence of even minor side effects was very low (3.5%) in the patients with endogenous depression. Orthostatic hypotension was observed in a few paitents. Some of these had low systolic pressures prior to therapy, and, in a few cases, unusually large doses of the drug probably were responsible. This was not an indication for stopping therapy, since usually it disappeared within a few days or after reduction in the dosage of the drug. In a few cases, constipation was noted and controlled with mild laxatives.

Most of the side effects were noted in the schizophrenics—hypotension, hypertension, headache, nausea, drowsiness, hyperexcitement, constipation, and dizziness.

DOSAGE

The usual starting dosage for most patients is 45 mg. daily, given in 3 divided doses (tablets contain 15 mg. each). If there is no response within a week, 15 to 30 mg. may be given at bedtime (bedtime is suggested because a few patients experience or-

10. Kimbal, R. W., et al., Presented before the American Academy of Neurology, April 18, 1959.
11. Ben, M., et al., *Personal Communication.*

thostatic hypotension at this higher dosage). After a maximal clinical effect is noted (usually within 1 to 3 weeks) the dosage is reduced gradually over a period of several weeks to a maintenance level that must be individualized. Usually it will be 15 mg. daily or every other day.

A few patients probably will require therapy for an indefinite period of time. In most instances of endogenous depression the patient will go into remission, and administration of the drug can be stopped after several weeks or months of treatment.

PHENELZINE AS A DIAGNOSTIC AGENT

The lack of toxicity of phenelzine leads to the suggestion that it be used as a diagnostic agent. Clinical trial of the drug in all cases of moderate to severe depression appears to be justified because such cases frequently have mixed etiologies that make it difficult or impossible to judge which ones will respond favorably. Administration of phenelzine should be continued for at least three or four weeks. This procedure may have particular value in cases of larval endogenous depression, where the diagnosis is often not obvious.

CONCLUSIONS

Phenelzine, β-phenylethylhydrazine, is active *in vitro* and *in vivo* as a potent, long-lasting, rapidly-acting inhibitor of monoamine oxidase. It is completely absorbed when given by mouth. The great majority of patients with endogenous depressions respond favorably to the drug, and only a small minority of such patients will need ECT. The freedom from clinically important side effects, and the specificity of the drug for endogenous depressions, make it possible to use phenelzine as a diagnostic measure. Since all clinical forms of depression may be complicated by the presence of an endogenous component, this procedure seems to be justified.◀

Herpes Simplex

Acute primary herpes simplex usually is seen as the typical cold sore or fever blister in the child or young adult. If the eye is the site of the primary infection, the picture is one of acute, violent, follicular conjunctivitis, with corneal erosions coalescing in the typical dendritic pattern and healing with a slight scar in 2-3 weeks. A circulating antibody titer can be obtained in 30 days, reaching its peak in 60. Recurrent infection is seen most commonly as dendritic ulcer of the cornea, but also as disciform keratitis and metaherpetica (i.e., diffuse breakdown of corneal epithelium from chronic herpes). Treatment of these infections remains a problem not solved by any of the antibiotics or chemotherapeutics now available. For dendritic ulcer, the cornea is anesthetized and painted with half-strength tincture of iodine. Neutralization of this with cocaine is followed by instillation of atropine and an antibiotic. The eye is occluded and medication given to control pain. Cortisone is contraindicated. If symptomatic therapy of disciform keratitis or metaherpetica fails and the eye seems progressisng toward blindness, irradiation should be tried. Of 36 patients with chronic herpetic lesions of the cornea, 6 were relieved and 17 improved by irradiation.

Gill, T. M., *Minnesota Med.*, 41:541-543,1958.

ORIGINAL ARTICLE

Tension Fatigue States: Treatment with Phenelzine

The response was uniformly good with minimal side effects in 80 per cent of 85 patients treated

HERMAN A. DICKEL, M.D., HENRY H. DIXON, M.D., JAMES G. SHANKLIN, M.D., and HENRY H. DIXON, JR., M.D.,
Portland, Oregon

Among the most prevalent disturbances of our times are the various conditions known as "tension states" or by some such name which implies that the underlying disturbance is the presence in the patient's life of increased "tension" either within the person or in his environment. Often, perhaps usually, considerable fatigue, exhaustion and depression accompanies this tension. Many clinicians like to call these cases "reactive depressions" but we like the expression "tension fatigue states," for they are often like the wartime "combat or operational" fatigue states. We will relate our experiences in handling a large number of these cases and indicate the value of the monamine oxidase inhibitors in alleviating the symptoms of certain cases not benefited by drugs given previously.

Over a period of years we have been interested in the problems of chronic neuro-muscular hypertension, fatigue and depressed states,[1-3] and we have felt that fatigue was

1. Dickel, H. A., et al., *Canad. M.A.J.*, 72:1-6,1955.
2. Dixon, H. H., et al., *West. J. Surg.*, 6:338-341, 1954.
3. Dickel, H. A., et al., *Ann. New York Acad. Sci.*, 67:780-787,1957.

frequently a state of physiologic depletion following prolonged states of neuro-muscular hypertension. We see a large number of these cases in our private practice. It is apparent that states of tension, tension and fatigue, and tension and fatigue with depression, are a common problem to most physicians.[4]

NATURE OF THE PROBLEM

The changes that must take place in such a patient are long range, which will so modify the mode of reacting to environment that he can live relatively symptom-free, obtaining the stature, the maturity, and the physiologic and/or psychologic changes that will allow him to be symptom-free. Most of these people are capable of making this sort of improvement, but are unable to do it on any immediate basis, because of the amount of distress they have. Psychotherapeutic programs are often weeks and months long. Patients who are tense, anxious, fatigued and depressed are occasionally able to take the time to be away from work, to recuperate and recover, but the vast majority are employed people who must be on their jobs if possible.

For this group of people, real benefit has come from relaxants and tranquilizers, providing these drugs did not interfere with normal cerebration and working ability. But, too frequently, patients put off the long-range plans for full and complete therapy if the tranquilizers were over-used.

DEFINITIONS AND DIAGNOSES

We use the expression "tension" to mean "neuro-muscular hypertension."[5] Irrespective of the symptoms, whether physical, emotional, psychological or intellectual, to make a diagnosis of this chronic state we must find objective evidence of neuro-muscular hypertension in the patient as well as the other physiologic symptoms accompanying tension. To accomplish this we routinely do electromyographic studies of our patients. Patients who have suffered from tension over a long period of time develop mood changes, marked anxiety, depression, etc. The presence of tension, of anxiety, of fatigue and/or depression, invariably interferes with any smoothness in a therapeutic program. It is imperative that the clinician alter some of these symptoms by using pharmacological agents. He must maintain a therapeutic relationship with the patient over a long enough period of time if he is to convince the patient a long-range plan is to benefit him permanently.

AN ILLUSTRATIVE CASE

A man of 38, physically well, referred for treatment. He had complained for 6 or 8 months of increased irritability, nervousness, insomnia, worry and concern that bouts of pain or distress in his abdomen and chest might mean early ulcer or some cardiovascular disturbance. He has periods of marked fatigue and irritability. Even with sedation he sleeps restlessly, and has not got much out of his vacation for several years. A junior executive in a local mercantile company, he has had to attend many executive sessions, has traveled some 50,000 miles in the last 3 years on special trips for his employers, and has often attended from 2 to 3 sales meetings a week. He

4. Cleghorn, R. A., & Curtis, G. C., *J. Canad. Psych. A.*, 4: Spec. Supplement, 513-523,1958.

5. Jacobson, E., Progressive Relaxation, University of Chicago Press, Chicago, Ill., 1929.

is 5'11½", weighs 182; has given no evidence of physical disease. Blood pressure is 144/88, some recent weight gain. The electromyographic tracings showed typical patterns seen in "the tension state." He has hesitated to do anything about his problem since finding out that he was "physically well." He has hesitated to cut down in his work, or to mention to his family that he was suffering. He is an unusually intelligent, hard-working man who might be considered a "neurotic type," but could be described as a rather typical "junior executive" who is exhausting himself because of the tension and fatigue that develop in his pattern of life. He came in and placed himself under treatment, that he might have something done to alter his approach to living. He recognized that any program would take a period of months to succeed. He welcomed relief during the first 2 or 3 weeks.

MANY DIFFERENT DRUGS USED

Over a period of years we have utilized a variety of drugs in handling these cases. The tranquilizers, the muscle relaxants, the cerebral stimulants, the euphoriants, have all been tried with questionable value to the long-range program.[6] Too frequently when immediate relief is obtained the long-term therapeutic program is forgotten. Fatigue, too, has often been a subject of concern to clinicians because these drugs, although valuable as adjuncts, do not get at the root of the trouble. The use of cerebral stimulants does not improve the patient, who assumes that he is more hopeless than had previously been recognized. Serious depressions and suicides have often resulted.

6. Lemere, F., & Lasater, J., *Am. J. Psychiatry*, 114: 655-656, 1958.

DRUGS ONLY RECENTLY AVAILABLE PROVE EFFECTIVE

Within recent months, we have noted that the monamine oxidase inhibitors, as a group, are effective in altering the physiologic depression and retardation often present in individuals under tension. The work done by a variety of people already indicates that these agents are effective in depressive states.[7] We felt that it would be of value to try these substances in a large number of our cases which could not, in every instance, be called "depressions" but did manifest feelings of depression on the basis of their tension and fatigue. Again, some clinicians might call these "reactive depressions," but we designate them as tension, fatigue, and feeling of depression which was a result of other disturbances.

REPORT ON NARDIL IS MOST FAVORABLE

Over a period of several months, we made clinical use of a variety of the monamine oxidase inhibitors. We are reporting on phenelzine,* the only one of the four we used, which produced the results we felt truly beneficial to this type of patient. We here include only those patients with tension fatigue states who were working at their usual tasks and able to follow our advice that they undergo a long-range treatment re-educative type of psychotherapeutic program, and let us use the medication only to make easier the first 2 or 3 weeks. The total cases in this study was 85 (Table 1), the oldest patient was 75, the youngest 16. All of these (32 men, 53 women) were either students in school, housewives, or do-

*Nardil®, Warner-Chilcott Laboratories, Morris Plains, New Jersey.

7. Sainz, A., The Phrenoproxic Activity of a Non-Noxious Anti-Depressant, J. Am. Psych. A., In press.

TABLE 1

RESULTS OF TREATMENT WITH *NARDIL*

Number of Patients	Significantly Benefited	Minimum Change	No Change	Side Effects
85	68	12	5	2
100%	80%	14.2%	5.8%	2.3%

TABLE 2

PATIENTS PREVIOUSLY ON OTHER OXIDASE INHIBITORS

Number of Patients	Significantly Benefited	Minimum Change	No Change	Side Effects
36	12	14	10	18
100%	33.3%	38.8%	27.9%	50%

ing other regular work, professional, semi-professional, or skilled. They all had a long history of tension and anxiety, with resulting fatigue, and the typical symptoms noted above. The dosage on these cases was 15 mg. of Nardil 3 times a day, continued until either benefit was evident or no benefit was to be hoped for. In case of benefit, the dosage was cut down to 10, then to 5, and a week after, out altogether. None of our patients have taken Nardil for longer than 4 weeks, and all of them usually took it about 1 week before deriving any benefit from it. If no benefit was obtained in 3 weeks we discontinued the drug.

ANALYSIS OF RESULTS ACHIEVED

As noted in Table 1, the percentage of patients markedly improved was 80 and of those improved but little 14.2, while but 5.8% were not benefited. It is important to point out that only 2 reported any adverse symptoms, and no unpleasant effects lasted long enough to be significant. Table 2 illustrates that 36 of these 85 patients had been tried on other monamine oxidase inhibitors by other physicians or ourselves.

Our own objective evaluation of these cases coincided with the improvement reported by the patients. In order to evaluate better the response of these patients, we have done EEG, electromyographic, or certain psychological tests on many of them. These tests could only be done on a sampling basis all through the series, since we are dealing with private patients who are working. Therefore, we are not herein reporting the statistical findings of test results, but simply indicating that enough of these have been done to indicate that they, too, bore out the fact that the subjective and objective findings of the improvement in these cases were sufficiently close to cause no significant changes in our findings.

The use of phenelzine as a temporary measure to improve these patients was remarkably good. In almost all cases two changes were noted first. The improvement in feeling tone with less fatigue and/or depression, and a considerable degree of reduction in the basic tension, appearing in from 3 to 5 days. Most signifi-

cant was the improved ability of the patient to accept, deal with, and accomplish the requirements of psychotherapy. We cannot report on any patients who took phenelzine without psychotherapeutic procedures, for we insisted before giving this drug that we would see the case often enough to carry on psychotherapeutic procedures. Also, we made sure that the evaluation of the need of the drug was made by us and not by the patient. At all times the drug was dispensed on a day to day basis, so that the patient had only an amount to last until the next visit, usually in one or two days.

During the time that we have used this drug, we have not seen any side effects last more than 1-2 days. Some few people would notice a very mild "let down" after the first 2 or 3 doses, but this is usually seen in people recovering from tension, and we felt that the complaint was not due to any adverse effect of the drug. There were no skin rashes, no central nervous system side effects. The two patients showing side effects complained for 1-2 days of mild gastrointestinal irritability.

CONCLUSION

We are reporting the use of one of the monamine oxidase inhibitors phenelzine on 85 patients with tension, fatigue and often depression, who were seen over a period of several months for psychotherapeutic procedures. Of these cases, 80% showed excellent benefit in that there was lessened tension, definite antidepressant action, and a normal feeling of well-being which in no way interfered with the patient's livelihood. All effects were uniformly good and no side effects were noted of any consequence. Moreover, in those instances where the drug produced no real benefit, there were no unpleasant or unwanted effects. We noted frequently that although phenelzine at times had no antidepressant effect, it nonetheless substantially improved the patient's ability to profit by psychotherapy.◀

Protein-Sparing Effect of Androgenic Hormones After Gastrectomy

Utilization of proteins was investigated by means of balanced studies in 31 patients who had been subjected to gastrectomy. These studies required 10 to 45 days. Thirteen of the patients were treated with androgenic hormones, and 18 were not treated. The utilization of proteins improved in all but 1 of the male patients treated with testosterone propionate. A lower dose of the agent, combined with estrogens, improved the nitrogen balance in a woman patient. Those receiving hormone treatment consumed an average of 2355 calories a day and gained an average of 8½ lbs. in 30 days; the figures for the 18 patients not receiving this therapy was 2740 calories, and 3 lbs. The increase in weight continued when, after discharge from hospital, the patients were given maintenance doses of testosterone phenyl propionate. There were no unpleasant side effects. Androgenic hormone therapy can be recommended for patients with impaired nutritional status as a result of total or partial gastric resection.

van Wayjen, R. G. A., et al., *Nederl. tijdschr. geneesk.*, 102:2413-2422,1958.

ORIGINAL ARTICLE

Hypogammaglobulinemia

This disorder, the basic cause of infectious diseases in 8 per cent of children, is effectively managed by replacement therapy

JACOB M. SOBOL, M.D., *Phoenix, Arizona*

One of the most puzzling features of pediatric practice is the child presenting a succession of infections that fail to respond to what would seem to be adequate therapy. Experience is here presented pointing to a deficiency of gammaglobulin, or a lack of some essential antibody factor in those with apparently normal levels, as a common host-defense deficiency. Frawley had predicted this 10 years ago in his appeal for "more studies on the value of immune serum globulin in the prophylaxis and treatment of certain infectious diseases."[1]

DEFINITION

The clinical picture of agammaglobulinemia is well recognized.[2] Hypogammaglobulinemia is similar in its manifestations, but has not been recognized with sufficient frequency in patients who suffer from repeated bacterial infection, although attention has been called to it.[3] Further, some children present the picture of hypogammaglobulinemia without deficiency of this plasma fraction. Clinically, the diagnosis of hypogammaglobulinemia should be established by the response to the administration of gamma globulin. This is borne out by various reports that in severe infections, unresponsive to antibiotics or chemotherapeutic agents, the simul-

1. Frawley, J. T., *Texas J. Med.*, 44:361,1948.

2. Bruton, O. C., *Pediatrics*, 9:722,1952.
3. Barrett, B., & Volwiler, W., *J.A.M.A.*, 164:866, 1957.

taneous administration of gamma globulin resulted in cure in a high percentage, although there was no evidence of a gamma globulin deficiency.[4,5,6]

For the purpose of this report, agammaglobulinemia is the absence or only minute presence of gamma globulin, presenting a clinical picture of extreme susceptibility to bacterial infection. In hypogammaglobulinemia the clinical syndrome is similar to that of agammaglobulinemia. Laboratory determination of serum gamma globulin separates the rare agammaglobulinemia from the large body of hypogammaglobulinemias.

The cases reported here do not all meet the criteria for hypogammaglobulinemia as measured by accepted laboratory methods and standards,[7] diagnosis here being largely clinical and not necessarily ruled out by normal, or even high, gamma globulin findings if clinical improvement was brought about by administration of gamma globulin. Following this concept, diagnosis of many common, acute, and recurrent childhood infections can be thought of in terms of the infection itself as well as in those of the response established by administration of gamma globulin.

MATERIAL

All 200 patients studied were found to have hypogammaglobulinemia by these standards. Of these, 4 boys and 4 girls were designated as having agammaglobulinemia. The remainder showed serum values of 0.015 up to 1.67 gm.% of gamma globulin, and because diagnosis in these cases rested upon their extreme susceptibility to infection, several other interesting diseases became automatically included in this study.

The patient types and infectious disorders observed are classified as follows:

1. Patients with frequently recurring bacterial infections responding poorly to vigorous use of antibiotics and probably waxing and waning according to the antibiotic blood level rather than actually clearing.

2. The puny infant whose development lags for some reason not evident, and whose respiratory infections begin early in life. Failure to gain weight is usually blamed on the infections. Most of these infants are in the age range of 3 to 16 weeks and constitute a fair proportion of this series. An infant in this category needs gamma globulin just as surely as does a patient at any other age with hypogammaglobulinemia. Another group of infants observed became seriously sick without adequate insult, e.g., an otitis media with prostration. A number of sudden deaths reported in infants of this type during the first 5 months have been associated with hypogammaglobulinemia.[8,9] Although a rampaging respiratory infection was the immediate cause of death in these cases, the paucity of symptoms is possibly explained by failure of the defense mechanism.

3. The whiny, delicate, easily tired child, particularly one with multiple congenital anomalies. Also the "angelic child" with not enough ambition to disobey, to investigate, to get into trouble. Cases of obscure fever and pain are included; also children with febrile convulsions, and a small num-

4. Harris, J. R., & Schick, B., *J. Mt. Sinai Hosp.*, 21:148,1954.
5. Fisher, M. W., *Antibiotics & Chemother.*, 7:315, 1957.
6. Waisbren, B. A., *Antibiotics & Chemother.*, 7:322, 1957.
7. Oberman, J. W., et al., *New England J. Med.*, 255:743,1956.
8. Spain, D. M., et al., *J.A.M.A.*, 156:246,1954.
9. Personal communications and subject of current studies.

ber of those in the first two years who faint without adequate cause.

4. Diseases of unknown etiology such as subendocardial fibroelastosis, Still's disease, mucoviscidosis, a number of cases of pseudo-rheumatic disease, and severe asthma of the infectious type responding to regular injections of gamma globulin.

Suspicion was based on unusual susceptibility to bacterial infection and poor response to antibiotics. Electrophoretic determination was made routinely for academic reasons, but diagnosis rested on the response to gamma globulin. Failure to respond dramatically was considered proof of adequate production and utilization of gamma globulin. Those with clinical hypogammaglobulinemia and normal gamma globulin, who made gratifying response to injection of gamma globulin, were considered as having adequate quantity but poor quality or poor utilization of gamma globulin or antibody. One case of leukemia and several of nephritis were treated concomitantly.

Electrophoretic examination was done every 6 months, and treatment discontinued if it indicated a normal gamma globulin level. If the patient relapsed, treatment was resumed for another 6 months. To date, 10 patients have been discharged as cured, including one with agammaglobulinemia.

Immunochemical tests done in a number of these cases were found useful in diagnosing agammaglobulinemia, but difficult to interpret in hypogammaglobulinemia. This difficulty may lie in the lack of information on the diversity and characteristics of antibodies, the concept of genetic antibodies such as those concerned in blood grouping, the possibilities inherent in the idea of immunologic paresis from a particular infection, and the congenital aspects of the problem.

Dosage of gamma globulin was determined by trial-and-error, the size of the infant's buttocks being a determining influence at first. Although in agammaglobulinemia a dosage schedule may be easily determined as outlined in the classic papers of Janeway and Gitlin,[10,11] these can serve only as a rough guide in "hypo" cases.

TREATMENT

The procedure followed in most instances was to start with a dose of 2.0 ml. a month in neonates and increasing this to 3.0 to 5.0 ml. in later months, depending upon weight and severity of illness. Correspondingly larger dosages, up to 10.0 ml., were employed in older children. During subsequent months the dose was adjusted until optimum results on minimum dose were obtained. Little difficulty in this connection was encountered because results were so clearly defined. If results had been only fair, an increased dose, usually 1.0 ml. per month as a trial would have been indicated. Conversely, if the initial dose brought desired results, succeeding doses would be reduced by decrements of 1.0 ml. until signs of deficiency were shown again, at which time the last dose would be increased by 1.0 ml. This is patently a trial-and-error method, but satisfactory.

The current infection must be treated adequately with antibiotics, as well as with gamma globulin. This report deals with the use of gamma globulin alone as a prophylactic meas-

10. Janeway, C. A., et al., *Tr. A. Am. Physicians*, 66:200,1953.
11. Janeway, C. A., & Gitlin, D., Gamma Globulins, in Advances in Pediatrics. Vol. 9, Year Book Publishers, Inc., Chicago, 1957, pp. 65-136.

IT HAPPENS IN THE BEST NOURISHED OF FAMILIES

VITERRA®

meets the specific vitamin-mineral needs of every member of the household — select the form that suits the age and condition of each patient best

VITERRA CAPSULES—comprehensive daily supplement. Bottles of 100.

VITERRA TASTITABS®—can be chewed, dissolved, or swallowed. Bottles of 100.

VITERRA THERAPEUTIC—high potency formula. Bottles of 30 and 100.

VITERRA PEDIATRIC—for infants and small children. 50 cc. Metered-Flow bottle.

Selectively formulated by one of the major producers of bulk vitamins

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

re, in the sense that correcting the ypogammaglobulinemia will result n a normal ability to resist invasion y pathogenic bacteria. Sinusitis roved the one infection which eemed to come and go, regardless of amma globulin levels. In this series f patients under adequate gamma lobulin therapy, most cases of febrile lness turned out to be attacks of cute sinusitis.

ESULTS

Very few treatment measures vailable to the physician yield such ecisive results as the adequate use f gamma globulin in these cases. ypogammaglobulinemia is fairly ommon and the despondent attitude f parents is most depressing. That ere-we-are-again-and-why-are-we--bedeviled family is a common exerience in every medical practice, nd these are the most grateful parnts that one is likely to encounter.

These patients become normal; ey no longer are made ill by every ay germ they encounter. Appetite, evelopment, enterprise, and resilice in these children became the me as in normal children. They frequently remained uninfected when rrounded by illness in the family. e parents reported that while the ildren did occasionally "catch cold" ey recovered in a day or two. One other stated that her child "looks tter out of his eyes"—a descriptive lloquialism. Improvement in temrament was almost always reported, ile complaints of abdominal pain d various aches and discomforts ased. In short, the children became althy. It was not unusual to hear mments from their school teachers this effect.

Most patients did well on a schedule of one injection every 30 days. A few could go several days longer, but many trying to do so contracted respiratory infections. Several cases required shorter periods, although none were under 26 days. One girl with Still's disease reverted to enuresis 4 days prior to the time her injection was due and got a bit "mean," but otherwise remained well. All this cleared the day after the injection. One baby with muscoviscidosis began to wheeze about five days before her injection was due. These cases illustrate the rule-of-thumb manner in which the need for continued therapy is gauged.

An impressive statistic is that 31 of the patients were hospitalized in a total of 1,057 patient-months prior to institution of gamma globulin therapy, while following the supportive use of gamma globulin only one hospitalization occurred from among these same cases in 723 patient-months.

The electrophoretic studies, repeated in each case at intervals of 6 months, showed an average of 0.4 gm.% rise in the gamma globulin titer per year. However, these figures did not warrant as much optimism as would seem to be indicated, first, because the rise in titer at the beginning of treatment was slow in some of the more severely affected, and second because there seemed to be a number of different types of hypogammaglobulinemia, not clearly definable at present but falling roughly into essential and transitory classifications. The latter recover after a few months on exogenous gamma globulin. Until five months prior to this report, there was no densitometer used in the interpretation of the electrophoretic strip. The values yielded by

this instrument were fairly consistently lower than those previously arrived at. It would seem proper to defer such an important conclusion as the rate of recovery until more of these cases have been studied more completely.

SUMMARY AND CONCLUSIONS

1. Hypogammaglobulinemia is a clinical diagnosis.

2. The incidence of hypogammaglobulinemia, or an immeasurable qualitative deficiency causing the same clinical syndrome, is high (8%) and is basic to most cases of frequent infection in childhood.

3. The incidence of hypogammaglobulinemia is much higher than that of agammaglobulinemia.

4. Most of these patients do not respond to antibiotics during infection as well as do normal children, unless gamma globulin is given concurrently.

5. There is no clear correlation between gamma globulin level and severity of the clinical syndrome, except in agammaglobulinemia.

6. The incidence is particularly high in children with multiple congenital defects.

7. A familial trend was noted in most cases.

8. These children need exogenous gamma globulin and do extremely well on a monthly maintenance dose.

9. An impressive percentage of children with infectious type of asthma benefit from adequate doses of gamma globulin used prophylactically.

10. A number of rare and ordinarily hopeless diseases found associated with low gamma globulin responded very well to administration of gamma globulin. They should be investigated in large enough numbers to yield valid data.

11. Enough is known to warrant use of gamma globulin during the first 6 months of life to prevent unexpected death from baffling pulmonary infection without heralding symptoms. It is suggested that a large-scale program by regional segments would yield most information on this point.

ADDENDUM

In the two years elapsed since the compilation of the above observations, the following points have been repeatedly noticed most consistently:

1. A 'let-down phenomenon' has manifested itself as the one most reliable criterion for estimating need of continued gamma globulin therapy. The parents describe a sudden cessation of well-being and activity at a point varying between five and two days before the next injection of gamma globulin is due. The patient has been described as becoming less ambitious, droopy, lack-luster and whiny. This situation clears up within a day or two after the injection. A number of children have been graduated from the program when this 'let-down phenomenon' ceased to be apparent and before their gamma globulin titer had reached what is considered quantitatively normal levels. These children got along very well without any further gamma globulin. However, those who continued to manifest this 'let-down phenomenon' have not been able to get along without gamma globulin regardless of the quantitative findings on electrophoresis.

2. There has not been a single adverse reaction nor any ill effects in any of the children treated in the

series attributable to the gamma globulin.

3. Children in this program have developed chicken-pox in an extremely mild form. Most of those who gave a history of exposure to chicken-pox appeared to be protected entirely.

Since 1952, a mere seven years ago when the first case of agammaglobulinemia was first described by Bruton, a rather surprising lot of misinformation has accumulated in the medical literature. None of it is true, yet never a discussion on the topic passes without at least one of these fallacies being injected into the conversation. They are refuted as follows:

A. There are no reactions, no ill effects, no risk whatever.

B. The injection of gamma globulin is not any more painful than any other injection and less painful than most. The pain that may be elicited by an injection of gamma globulin is simply the pain that could be elicited by an equal volume of any fluid injected rapidly. With a little thoughtful experience one can give these injections without any pain.

C. There is no danger of hepatitis. Quite the opposite is true. Gamma globulin is used successfully to prevent and even cure early cases of hepatitis provided it is not used in homeopathic dosage. It is very interesting, however, to note that the hypothetical transfer of virus of serum hepatitis has been hung on the coattails of gamma globulin.

D. Suppression of endogenous gamma globulin production by the patient under exogenous gamma globulin therapy does not occur. Actually the opposite is true, as an endless series of electrophoretic studies over the past five years amply demonstrate.

E. The treatment with gamma globulin is not expensive when considered in a reasonable light. It is quite obvious that the type of case under consideration here will incur a greater expenditure of money in medical and pharmaceutical bills than will the same patient receiving one injection of gamma globulin per month.

F. There is no rational reason for giving gamma globulin injections every week or two, or on any schedule other than once a month. There are ample studies on the degradation rate of gamma globulin and its half-life which demonstrate the futility of any program other than the one outlined above.◀

Grateful acknowledgment is made to Sam T. Gibson, M.D., Director Blood Program, The American National Red Cross; to Philip A. Boyer, Jr., M.D., Director of Clinical Research, Pitman-Moore Company; and John W. Palmer, Ph.D., Vice President, Hyland Laboratories, for the generous supplies of gamma globulin which made this study possible.

Early Diagnosis of Purulent Meningitis in Nursing Infants

In 51 nursing infants with purulent meningitis, aged 3 days to 12 months, observed during a 5 year period, significant symptoms had developed by the 4th or 5th day of the illness. Fever was most frequent in those close to 1 year of age. Symptoms of intracranial hypertension appeared early in an inverse ratio to the ages. Meningeal irritation was evidenced early, most frequently in infants of 9 to 12 months. Brain involvement was most frequent in the youngest, being present in 60 to 75% of children in the first 48 hours of illness.

Rottini, G., *Minerva pediat.*, 10:1388-1398,1958.

For the best results from antihypertensiv therapy: add Esidrix

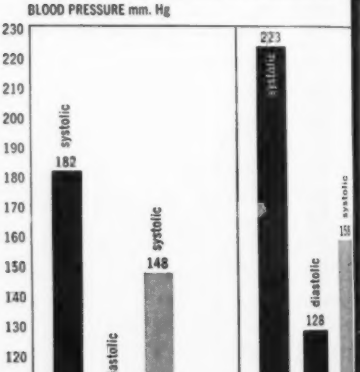
(hydrochlorothiazide

THE ANTIHYPERTENSIVE POTENTIAT

Esidrix, through its unique effect on body salts,* provides a physiologic environment in which antihypertensive drugs work best. Thus Esidrix, when added to any treatment program:

1. Safely reduces blood pressure to the lowest levels yet achieved with oral therapy.
2. Often reduces blood pressure in patients resistant to previous therapy.
3. Minimizes side effects by reducing dosage requirements of other drugs.
4. Promotes diuresis in patients with edema.

Potentiating Effect of Esidrix on Se



*Esidrix is at least 10 times more active than chlorothiazide and g increases sodium and chloride excretion; however, it has no more eff potassium excretion than does chlorothiazide.

ORIGINAL ARTICLE

Some Clinical and Pharmacological Aspects of a New Skeletal Muscle Relaxant

This drug appeared to accelerate a return to mobility in a majority of patients with neuromuscular disorders

OSCAR F. DAVIS, M.D., PH.D., ALBERT J. LEVINE, M.D.,[1] CHARLES BECK, M.D.,[2] and BERNARD HORWITZ, M.D.,[3]
Chicago, Illinois

A therapeutic goal shared by investigator and clinician alike is the desire for restricted and predictable drug action. This goal only infrequently obtains, thus the treatment of hypertension may be fraught with G. I. tract disturbances (blocking agents), while the use of psychotropic drugs is often followed by neuromuscular responses. In searching for specific activity, several new compounds were developed and studied. This report deals with the clinical evaluation of a CNS drug* with more singular activity, the pharmacology of which has been exhaustively investigated.[1]

PHARMACOLOGY

Potent anticonvulsive properties for styramate were made evident by observing the degree of protection af-

1. Department of Internal Medicine, Chicago Medical School; Mount Sinai, Cook County and Edgewater Hospitals.
2. Department of Internal Medicine Stritch School of Medicine and Mercy Hospital, Chicago, Ill.
3. Department of Surgery, Edgewater and Elgin State Hospitals.

*Sinaxar®, brand of Styramate, Armour Pharmaceutical Company, Kankakee, Illinois.

1. De Salva, S. J., et al., Pharmacological Studies on a New Skeletal Muscle Relaxant, 2-hydroxy, 2-phenyl ethyl carbamate, Publication in preparation.

forded against electric shock, strychnine and Metrazol. Unlike the general CNS depressant phenobarbital, styramate (like Mephenesin) blocks Metrazol-induced extensor tonus and delays or prevents death, but does not appreciably attenuate the time of onset of convulsions. In test doses of 25 mg./kg. the patellar reflex was inhibited by styramate for 134 minutes, whereas identical doses of Mephenesin produced inhibition for only 40 minutes. Styramate 150-450 mg./kg. per os, and 150-350 mg./kg. subcutaneously did not change the blood pressure in the anesthetized and unrestrained rat. Smooth muscle was not influenced as demonstrated by isolated rat colon and guinea pig ileum experiments with 200/ml. concentrations of styramate.

ACUTE TOXICOLOGY STUDIES

The results of oral toxicity studies on mice and rats (mg./kg.) are as follows:

SPECIES	LD_{50}*
Mice (female)	1240
Rat (female)	1425
(male)	1300

*LD_{50}—Lethal dose in 50%

In the dog, intraperitoneally, 400 mg./kg. caused ataxia, retching and defecation, with 1200 mg./kg. paralysis of the skeletal muscles, and surgical anesthesia was induced without loss of corneal reflex. Orally, at a 720 mg./kg. dose level, there was some salivation, vomiting and depression. Five six-month-old New Zealand white female rabbits were force fed daily, for 11 days, 300 mg./kg. styramate in 1% gum tragacanth suspension. Hematological and macroscopic examinations of heart, liver, spleen, kidney, adrenals, gastro-intestinal tract, and urinary system revealed no pathological effects attributable to styramate.

CHRONIC TOXICOLOGY STUDIES

Female and male rats (60 to 80 gm. at the start of the experiments) were treated for 3-, 6-, and 12-month periods. Groups of 56 rats each (half females and half males) received 30, 90 and 270 mg./kg. daily in their diet. A fourth group was force fed with 270 mg./kg. Hematological examination revealed no blood dyscrasias and the urinalyses were negative. Macroscopic and microscopic examination of the viscera revealed nothing pathological attributable to the drug.

Twenty-four dogs were divided into four groups: three receiving 180, 360, and 720 mg./kg. daily, respectively, the fourth serving as a control.

Hematological examinations, urinalyses and blood examination (hemoglobin, glucose, non-protein nitrogen, icteric index, total protein and bromsulphalein) were negative. Histological examination of heart, liver, kidney, stomach, duodenum, testes, ovaries, uterus, spleen, adrenal, thyroid and lungs did not show any pathological changes which may have been caused by the treatment. In all species studied, styramate induced a motor paralysis, which, according to all evidence does not seem to be due to myoneural involvement. The polysynaptic blocking effect without abolition of the knee jerk, the lack of action against strychnine convulsion, and death imply that styramate acts through a central mechanism.

Moreover, styramate showed a favorable therapeutic index against supramaximal electroshock, subcutaneous Metrazol and strychnine induced seizures in mice. There were no cumulative or toxic effects with high doses

rel eves painful muscle spasm, improves
mc bility, facilitates rehabilitation...

PARAFLEX®

Chlorz zone*

PARA EX provides effective skeletal muscle relaxation for about 6 hours with a 1- to 2-tablet dose. relieves pain and stiffness and improves function in a wide variety of ortho dic, arthritic, and rheumatic disorders. It may be used alone or with other agents indic ed in the management of skeletal muscle spasm. It is especially valuable when sed in conjunction with physiotherapy and other rehabilitative procedures. Side effect re rare, almost never require discontinuance of therapy.

Dosag ADULTS—1 to 2 tablets three or four times a day.
CHILDREN—½ to 2 tablets three or four times a day, depending on age and weight.
Suppl : Tablets, scored, orange, bottles of 50. Each tablet contains PARAFLEX, 250 mg.

*U.S. P nt Pending 255C59

McNEIL
McNeil Laboratories, Inc.
Philadelphia 32, Pa.

TABLE 1

COMPARATIVE INFLUENCE OF STYRAMATE IN ACUTE BACKACHE

Treatment	No. of Patients	Restored mobility in 2 days	Moderate mobility in 2 days	Restored mobility in 5 days	Indifferent response in 5 days	Untoward Reaction
Styramate, 200 mg. q.i.d. vs. backache without disc disease	84	64	8	5	7	2
Styramate, 200 mg. q.i.d. vs. backache associated with minor disc disease	26	16	4	2	4	1
CONTROLS (all vs. backache without disc disease)						
1. Meprobamate, 400 mg. q.i.d.	17	5	5	3	4	1
2. Physiotherapy plus Bed Rest	15	3	7	4	1	0
3. Styramate plus physiotherapy and Bed Rest	22	18	3	1	0	0

in the chronic studies with dogs and rats, nor any blood dyscrasia, or microscopic pathological organ variation.

In comparison with other central depressants, styramate appears to be a more specific muscle relaxant. Styramate compared to Mephenesin has a threefold longer duration of activity. Concurrent measurement of the EEG and spinal polysynaptic activity in cats demonstrated that styramate did not produce any sleep-like changes in the EEG at the dose levels which effectively reduced spinal polysynaptic transmission. There was no significant effect upon the blood pressure with styramate, nor was there any evidence of specific autonomic action as seen with reserpine and chlorpromazine.

CLINICAL STUDIES

One hundred and sixty-four adult patients of both sexes and varying ages were selected for study. In order to evaluate the skeletal muscle-relaxing properties of styramate in humans several diagnostic and comparative criteria were established. Carcinoma or other space-occupying lesions of the cord or vertebral column, radicular pain, etc., were ruled out, roentgenographically and by other clinical and laboratory means. Parkinsonism, with its rigidity and spasticity and certain other neuromuscular diseases were not considered in this evaluation. Our purpose limited the source of clinical material to two general groups:

1. Acute muscular spasm without disease of the nucleus pulposus.

2. Muscular spasm accompanying disc disease, as diagnosed roentgenographically and by the presence of Laseguе and other diagnostic signs.

Therapeutic efficacy of styramate 200 mg. q.i.d. was compared with

three groups of controls:

1. Meprobamate 400 mg. q.i.d.

2. Bed rest, plus hot wet packs, massage and infra-red rays.

3. The treatment in (2) plus styramate 200 mg. q.i.d.

The major treatment group, receiving styramate for a minimum of eight doses, consisted of 84 patients with acute severe low-back pain and immobility, and 26 patients with early roentgenologic evidence of minor disc changes accompanied by acute pain, presumably muscular.

In differentiating pathogenetically between these groups, it is difficult to determine whether pain is caused by destruction of muscle, or merely follows maximum and continued contraction, perhaps associated with myositis.

The three therapeutic control groups were formed by 54 patients with acute back pain (muscular). The results are reflected in Table 1.

DISCUSSION AND CONCLUSION

The interpretation of results presents several pitfalls which are not easy to overcome. One is based on the inability to quantitate the severity of disability at the onset of therapy. Nevertheless, control measures including comparison with the widely used skeletal muscle relaxant meprobamate seem clearly to indicate greater clinical efficacy for styramate. These clinical observations support the pharmacodynamic studies reported in animals. In this study there were no instances of hyperergic phenomena, CNS depression or bladder dysfunction.

Over 90 per cent of all patients receiving only physiotherapy and bed rest were almost completely recovered in five days. Thus the value of styramate t.i.d. is more graphically reflected by the recovery rate in the first two days in which groups the styramate induced response seems to be more than fortuitous, for, when styramate was added to physiotherapy and bed rest, the response was noted earlier in therapy.

Observations, combined with biometric analysis of the data encourages the conclusion that styramate favorably influences the course and severity of the illnesses studied. In spite of the shortcomings inherent in a clinical study of this type, the pharmacological data in animals and the results noted in man recommend this drug for further investigation.◀

Comparison of Intramuscular and Oral Vitamin B_{12} in Pernicious Anemia

Over a period of 2 years, 71 patients on a daily dose of 100 mcg. vitamine B_{12} by mouth, 1 hour before breakfast, was maintained at least as well as a group of 84 receiving a monthly intramuscular injection of 100 mcg. Thirty-four patients with pernicious anemia given intramuscular injection of 1,000 mcg. of vitamin B_{12} per month for 2 years showed no significant change in hemoglobin and red blood cell levels. There was no apparent advantage in a dose higher than 100 mcg. per month.

Hemsted, E. H., & Mills, J., *Lancet*, 2:1302-1303, 1958.

ROCHE

liscoverer of the therapeutic effects of the hydrazines...

irst to introduce the therapeutic era of amine oxidase regulators...

nnounces

A more active amine oxidase regulator

New Marplan

or the relief of moderate to deep depressions

clinically safer ▪ therapeutically more useful

Marplan in depression—Marplan exerts a otent therapeutic action in a variety of psychitric disorders with associated symptoms of epression, with or without withdrawal or repression.[1-5] By regulating amine oxidase levels, Marplan inhibits the breakdown of serotonin, orepinephrine and other biologically active nines which are postulated to have a role in ie normal function of various brain centers. his sparing action on biogenic amines may be ie mechanism whereby Marplan elevates mood id reverses the depressive symptomatology. Marplan is *not* a central stimulant of the amhetamine type. It is *not* in any way related to ie phenothiazine group of drugs *nor* to other anquilizer or sedative agents. Marplan is, inead, a metabolic cellular enzyme regulator hich opens a new sector in the field of psychic ydrazine therapy.

The clinical record of Marplan—Marplan has een under intensive clinical investigation for ore than a year. A broad clinical research proram continues to define the full range of Marplan's therapeutic applicability. However, ready almost 300 research clinicians have valuated Marplan in over 3500 cases.[1-8] Of is group, more than 2751 were patients with sychiatric and emotional disorders associated ith depression. In the 2449 fully evaluated ases, the greater majority (66.2%) showed gnificant improvement. "Depression of mood id somatic preoccupation were less pronounced, oncentration improved, irritability lessened and e patients appeared to be more relaxed."[2] Marplan was evaluated clinically for more than one year. In some patients, the beneficial effe appeared within several days; in most, with one to three weeks. In a few cases, response w not observed until after three to four weeks therapy. An example of an unusal result in chronic psychiatric patient is the following ca history from the Danvers State Hospital, H thorne, Massachusetts[3]:

40-year-old male schizophrenic. *First hospit ized 19 years ago. Continuously hospitalized the last 10 years. ECT and various phenoth zines proved ineffective. Patient's condit varied between catatonic posturing and acti stupor, and between extreme block and compl mutism. He had no apparent affect. On tre ment with Marplan (40 mg/day), he becam cheerful, talkative, no longer a feeding proble Now works in one of the hospital's departme and has ground privileges. Mental content a sensorium disclose no psychotic manifestatio at present.*

Incidence of side reactions—In one of t largest bodies of clinical material for this n class of drugs, Marplan shows one of the low recorded incidences of side effects. Particul attention was focused on attempts to define precisely as possible amine oxidase inhibi side effects on a wide range of organs, includi liver and bone marrow. Extensive clinical studi have revealed no jaundice or liver dam attributable to Marplan. Nevertheless, sin Marplan is an amine oxidase inhibitor, the sa precautions should be observed with Marp therapy as with other amine oxidase inhibito

ORIGINAL ARTICLE

Some Causes of Failure in the Treatment of Skin Diseases

Some methods of avoiding the many pitfalls encountered in therapy of dermatoses are discussed

KURT WIENER, M.D., *Milwaukee, Wisconsin*

The dermatologist frequently sees patients who have been treated with various medications, apparently without success. Sometimes the treatment made the condition worse, at other times dramatic improvements followed almost immediately after another doctor took charge. There are many reasons for the failure or success of dermatologic therapy, but often the causes are simple and attention to some seemingly trivial details may produce results.

IMPETIGO

Children or adults may have impetigo which fails to heal though the prescribed ointment is correct. The reason for the failure is simple. The patient or his mother has not been instructed properly how to use the prescribed ointment, or has not properly carried out instructions. The thick crusts have been covered with a thin film of ointment once or twice a day instead of a generous amount. Cotton swabs should be used to work the ointment in three times or as many times a day as is necessary. If the ointment is wiped off, the mother has to put on a new thick covering. Soon the crust will be loose and can be removed with a swab. It is essential that there be no let-

up with the ointment which would permit drying of the crust or formation of a new one. The mother should also be shown how to apply the ointment to infected nostrils by rotating movements of the cotton swab. She should be generous with tissues and swabs and not skimp with the ointment. If she follows these directions, the "resistant" impetigo will heal in a few days. Systemic use of antibiotics is rarely necessary, but it is of great help when there are many lesions or when there is great difficulty to treat them topically.

PSORIASIS

The general attitude of many doctors with regard to the treatment of psoriasis is pessimism which discourages the patient and weakens his efforts. We have no reliable internal treatment and can do little or nothing to prevent recurrences. However, a great deal can be done to cure the visible eruption. First it is necessary to treat the lesions, not just hand the patient a prescription or an ointment sample. Start with low concentrations and increase or decrease the strength according to the response. Regularity, persistence, and continual removal of scales are necessary.

Here is a time-proven way of treating psoriasis in large plaques: Apply dressings with copious amounts of 5 to 10% salicylic acid vaseline. Order daily warm tub baths with a handful of soap flakes and water rinse. This will remove practically all scales within two days. When the lesions appear red and no longer silvery, the antipsoriatic treatment starts with 0.1% chrysarobin in zinc paste, rubbed in gently twice daily using a soft tooth brush. To use the hand is apt to carry chrysarobin into the eyes causing conjunctivitis and even keratitis. The patient should wear old pajamas and sacrifice some old bed sheets because the stains from chrysarobin do not come out.

See the patient at regular intervals, every two weeks or every week, to see whether changes in treatment are necessary. If the scale formation and the itching diminish and no irritation occurs, he may continue with the same ointment for another week or two. If there is no further progress, the concentration of the chrysarobin ointment should be stepped up to 0.25, 0.5, or 1%, later even 5, 10, or 20% (on small areas). A frequent error is to let the patient finish using his no longer effective ointment. The greatest economy is to cure the patient fast, not to save a little ointment. It is the failure to keep the psoriasis "on the run" which most often causes disappointment and pessimism. If, at any stage of the treatment, the patient sees no progress, he thinks that the doctor cannot help and he becomes apathetic. If he is encouraged regularly by his doctor and if the strength of the ointment is increased, the patient will improve. If irritation occurs, chrysarobin should be stopped and zinc paste substituted for a few days.

OTHER DRUGS

Tars 1-10% in vaseline are messy and less effective than chrysarobin. The odor of tar is a great disadvantage if used on large surfaces. The tars often cause folliculitis and light sensitization on exposed parts, and may cause albuminuria from absorption. Ammoniate of mercury is clean but not so effective as chrysarobin. There is also the danger of sensitization to mercury and absorption from large surfaces. Although it is a second

postoperative

patient distress can be prevented...

COZYME™

(*d*-pantothenyl alcohol, Travenol)

A Routine Procedure for the Early Resumption of Postoperative Intestinal Activity

- effectively prevents and corrects abdominal distention . . . and retention of flatus and feces
- restores normal peristaltic activity, physiologically

because COZYME supplies the active molecular component of coenzyme A—pantothenic acid—which is essential in the formation of acetylcholine, the chemical mediator of nerve impulse transmission governing intestinal motility.

Supplied: COZYME 10 ml. multiple dose vial containing 250 mg. per ml. of *d*-pantothenyl alcohol with 0.45% Phenol added as preservative.

COZYME 2 ml. single dose vial containing 250 mg. per ml. of *d*-pantothenyl alcohol. 25 vials per carton.

TRAVENOL LABORATORIES, INC.

Pharmaceutical Products Division of Baxter Laboratories Inc.
Morton Grove, Illinois

1959. Hay-ock, C. E.; Davis, W. A., and Morton, T. V.: Am. J. Surg. 97:75-78 (Jan.) 1959. Stone, M. L.; Schlusser, S.; Silberma

best remedy, it is indispensable particularly on the face and hands and on the scalp either alone or with equal amounts of liquor carbonis detergens in a washable base (e.g., Aquaphor). It is irritating in combination with salicylic acid.

In psoriasis of the scalp in men, the hair should be cut as short as possible. The removal of scales with large amounts of 10% salicylic acid in a washable base (Aquaphor or Dermabase) or with one of the proprietary oily preparations (Riasol, Alphosyl) is necessary. Long hair has to be parted and the emollient applied to the scalp, avoiding the hair itself as much as possible, repeating this in a parallel line 1 cm. away. Loose scales should be combed out frequently.

FUNGUS INFECTIONS

There is a tendency to diagnose various vesicular or scaly eruptions of the feet as "a fungus" or "athlete's foot." Fungus infection produces interdigital vesicles which quickly burst and change into moist or scaly-dry surfaces invading only little of the dorsal aspect of the toes. On the arch area of the sole the horny layer is very thick so that the vesicles stay intact for a long time as yellowish or orange spots. Two common diseases of the feet to be differentiated from epidermophytosis are contact dermatitis and atopic eczema. In the former, the dorsa and the ankles are likely to be affected, the soles less. A good history and patch tests with regard to foot coverings and medications used for "athlete's foot" often clarifies the situation. Atopic eczema of the feet usually occupies the dorsa; there may be typical eczematous areas in the flexures of the knees and elbows, and a personal or family history of eczema, hay fever or asthma.

Microscopic examination of scrapings is a simple way to make a positive diagnosis of mycosis and repeated negative findings may rule out fungus infection. The finding of fungus elements which confirms the diagnosis frequently leads to wrong treatment. If there is much acute redness, vesiculation, oozing, pain or even lymphangitis, no fungicides should be used. The patient should rest with his feet slightly higher than the rest of the body—a position necessitating lying down.

Moist compresses, gently and slowly cooling by evaporation are the best treatment of acute inflammation of the skin. Pads of four layers of wet (not dripping) gauze are placed between the toes and then all the toes and a large part of the foot wrapped into four or eight layers of the wet gauze but otherwise left uncovered. The dressing must be replaced every two hours, at the same time removing debris and exudate. Saline solution, 3% boric acid, or 0.25% resorcin (aqueous) are satisfactory. If there is much exudation and oozing 0.05 to 0.1% silver nitrate solution in distilled water serves well. Lymphangitis in the acute phase requires bed rest and systemic use of antibiotics. After a few days of moist dressings and rest, the acute symptoms will have abated and the affected skin will be dry. Mild fungicides may now be used. Undecylenic acid salts and related chemicals (Desenex, Salundek) three times daily are good in the subacute or subchronic phases. After one or two weeks, stronger fungicides may be used. In the chronic stage only, 1 to 10% crude coal tar in vaseline, or 0.1% chrysarobin in zinc paste, or painting with 10 to 50%

liquor carbonis detergens in alcohol are good methods. The acute stages over, few patients continue treatment to complete cure.

There is hope that the new antibiotic griseofulvin will be more effective than external medication.

ACUTE CONTACT ECZEMA (DERMATITIS)

An ointment of 0.25 to 0.5% hydrocortisone or related steroids is excellent if used regularly, often enough and in sufficient quantity. It should be gently rubbed in 4 to 5 times daily at intervals of 4 hours. The high price may forbid it if large areas are involved. In extensive cases systemic treatment is more effective and more economical. As a rule, 40 mg. daily of prednisolone are necessary to make an adult patient with a severe case comfortable. In the hospital, 25 units of ACTH in 5% glucose by slow intravenous drip (20 drops per minute) is economical and highly effective. As soon as the most tormenting symptoms have abated, the dosage of steroids can gradually be reduced. It is a frequent error to stop too early and too suddenly. Even after the symptoms have completely subsided, a daily dosage of 10 and later 5 mg. should be given for a week or two.

Common mistakes in the treatment of dermatitis or eczema of known or unknown cause are the use of too strong medications in the acute and too weak ones in the chronic phases. Warm compresses or wet dressings are best in acute oozing eczema. Remember no impermeable covering! As soon as the surface is dry, a shake lotion of 20% each of zinc oxide and talcum and 30% each of glycerin and water may be used several times a day, sparingly, not thickly, because it is apt to cake. The remnants of the former coat do not have to be removed every time.

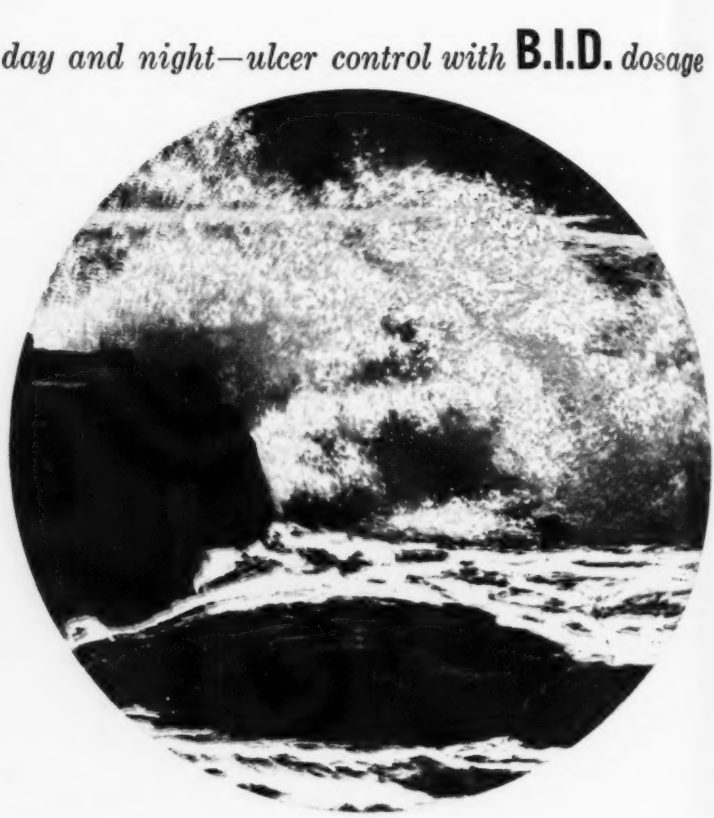
TOO MUCH CLEANSING

Cleansing measures have done more harm to inflamed skin than has neglect of these measures. Wet dressings obviate other cleansing. Lotions may be dabbed off with warm water once a day or every second day. It is not necessary to remove the last speck, although a thick residue may create a cleansing problem. Strong solvents such as benzene or carbon tetrachloride are permissible on small dry areas only, never on the scrotum. For large areas olive oil is best, although its application requires patience. Patients with acute eczema, especially of the hands, should not bathe or wash with water and soap. However, this is permissable in the chronic form. In eczema of the hands, prolonged contact with water, soap or detergents is harmful. A short washing in warm water with one of the soapless cleansers once or twice daily is permissible.

CHANGE OF TREATMENT WITH SUBSIDENCE OF ACUTE PHASE

When the symptoms of acute inflammation have abated, a paste of 20% each zinc oxide and talcum in vaseline is used. Ointments with a grease base such as vaseline or lanolin are last in the sequence. In some cases of contact dermatitis wet dressings, shake lotions or thin applications of paste suffice. In most cases, antieczematic medications have to be added. A frequent error is disregard of the rule of increasing strength. The following scale will suffice in many cases: ichthyol, 1-5%, in shake lotions and pastes; liquor carbonis detergens, 5-20%, in shake lotions; crude coal tar, 1-10%, in vaseline—in the order

day and night—ulcer control with **B.I.D.** *dosage*



Just one 10 mg. Daricon tablet in the morning, and one at night before retiring, keeps your patient free from the pain and discomfort caused by gastrointestinal spasm, hypermotility, and hypersecretion.

Daricon is a remarkably potent and well tolerated antisecretory/antimotility agent. Its *naturally* prolonged action provides day and night relief of pain and symptoms associated with peptic ulcer, functional bowel syndrome, biliary tract dysfunctions, and other gastrointestinal disorders characterized by spasm, hypermotility, and hypersecretion.

EVEN REFRACTORY CASES RESPOND

new **DARICON***

oxyphencyclimine hydrochloride

Pfizer *Science for the world's well-being*™

Pfizer Laboratories
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

References: 1. Finkelstein, M., et al.: J. Pharmacol. & Exper. Therap. 125:330 (April) 1959. 2. McHardy, G., et al.: Postgrad. Med., in press. 3. Winkelstein, A.: Amer. J. Gastroenterol., in press. 4. Finkelstein, M., et al.: Presented at Fall Meeting, Amer. Soc. Pharmacol. & Exper. Therap., 1958. 5. Leming, B.: Clin. Med. 6:423 (March) 1959.

*Trademark

named. Prescribe no more than is necessary; no tar in acute and subacute phases; 1-10% crude coal tar in vaseline is most useful in chronic eczema, but do not start with it. Liquor carbonis detergens is derived from coal tar, but it is less irritating, and a 5% shake lotion can be used early if there is no oozing. A common error is to treat widespread dermatoses with ointments instead of shake lotions. As long as there is improvement with a lotion, stick to a lotion. Often the dry skin seems to be in need of a lubricant, but the ointment frequently makes matters worse.

SCABIES NOW RARE BUT TO BE BORNE IN MIND

An exception is the treatment of scabies—now a rare disease. The most frequent mistakes in the treatment of scabies are failure to treat the whole body surface from the neck down and to treat the whole family whether they have symptoms or not. All body folds, the navel, the nipples and the genitals must be treated. An amount of 150 to 180 gm. of ointment is adequate for the treatment of an adult person for three days. Ten per cent sulfur in vaseline does not sting, and seldom irritates in three applications. The sulfur odor is only faint and the ointment is cheap.

DON'T EXPECT TOO MUCH OF ANY ANTIPRURITIC

There does not exist a really good topical antipruritic. A solution of menthol, 1-5%, and phenol, 0.1-1%, in 70% grain alcohol is effective on the unbroken skin especially in urticaria. It is not suitable in any acute inflammatory state. Eurax ointment is quite effective and rarely irritating. The ointments containing benzocaine and related anesthetics have little antipruritic effect and are notorious sensitizers. A common error is to use the "caine" ointments for too long a period, particularly around the anus.

The antihistamines once enjoyed a reputation as topical antipruritics, but few dermatologists are now using them. Washing with hot water or pressing a hot wet towel against the itching area gives temporary relief. In widespread or general itching such as senile pruritus, 5% liquor carbonis detergens, 0.1% menthol shake lotion is often satisfactory. Warm tar baths for 15 minutes give some relief. Since itching often starts when the patient is disrobed, his night clothes should be warmed and ready so that he is not exposed to even slight cooling.

RUBBER OR PLASTIC GLOVES

Protective rubber or plastic gloves should not be worn directly on the skin but with a clean white cotton glove as a liner. Rubber is a common sensitizer. Rubber gloves with a fabric lining may prevent the rubber contact, but the lining soon becomes dirty and able to carry the allergen, and also infectious material from pustules and scales. Rubber gloves should be long enough so that the allergenic liquid cannot splash easily over the edge and creep along the liner gloves. The pressure of the elastic outside glove may then intensify the contact with skin. Finally, to avoid maceration, rubber gloves should not be worn for a longer period than 20 minutes at a time.

CONCLUSION

Avoidance of the mistakes named, and use of the simple measures discussed, will heal a large percentage of the skin diseases which the physician encounters in his practice.◀

Like oil on troubl water

When smooth muscle spasm gets rough on your patients...

TABLETS • CAPSULES • ELIXIR

In each Tablet, Capsule or tsp. (5 cc.) of Elixir

Hyoscyamine sulfate 0.1037 mg.

Atropine sulfate 0.0194 mg.

Hyoscine hydrobromide 0.0065 mg.

Phenobarbital (1/4 gr.) 16.2 mg.

Prescribed by more ph

ORIGINAL ARTICLE

Lesser Skeletal Injuries of the Neck

Some newer methods of diagnosis of lesser skeletal injuries of the neck are presented and discussed

JACOB KULOWSKI, M.D.,* *St. Joseph, Missouri*

Increasing numbers of patients are being treated for injuries to the neck because of the mounting number of traffic accidents. (Fig. 1) The complex nature of the anatomical structures involved has resulted in clinical groupings of cases which are not widely known. There is a distinction between injuries of the soft parts (with "negative" x-rays), cord and nerve roots, and the spinal segments themselves.

In the absence of positive x-ray findings (among cases frequently presumed to have "sprains"), the road to diagnosis and treatment frequently becomes difficult. Improvements in radiologic techniques have been made which show minor and moderate skeletal injuries easily missed by routine methods.

The second class of cervical injuries include those of the atlas and axis. Their uniqueness may be attributed to the special configuration of these vertebrae. The lower five segments have supplementary intervertebral "Luschka" joints.

Cervical injuries may or may not be complicated by cord damage. There is no positive ratio between degree of skeletal injury and amount of cord (or spinal root) involvement. Complete dislocation of a vertebra may

*Author of "Crash Injuries, The Integrated Medical Aspects of Automobile Injuries and Deaths," being published by Charles C. Thomas, Springfield, Illinois. Figures 1, 2, & 4 are from this book.

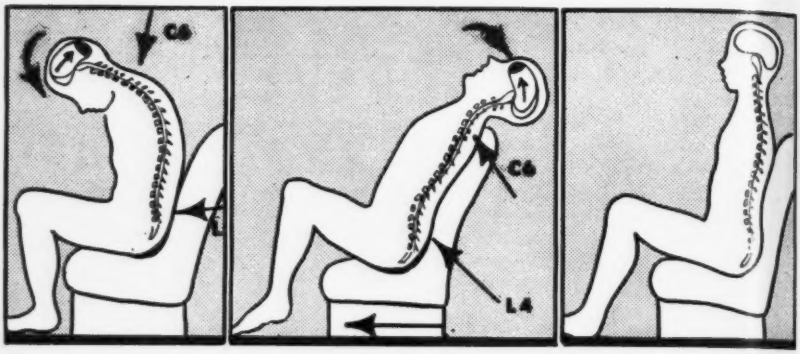


FIGURE 1

Mechanism of whiplashing cervical injuries due, in this instance, to rear-end collision (to be viewed from right to left).*

cause no paralysis; tetraplegia may result in a case without radiologic evidence of skeletal injury (the paralysis resulting from anterior pressure by herniated or ruptured nuclear material from the intervertebral disc or discs in some cases, or from hematomyelia). (Fig. 2)

In any case there may be subluxations and fractures of the elementary processes and structures of the cervical segments; lateral mass (apophyseal points and interarticular isthmus), laminae, and Luschka joints. Ordinary methods of examination often fail to show these minor-to-moderate injuries. Recognition of this failure led to the development of caudad and cephalad angled AP stereoscopic and magnification techniques. There has been a progressive effort over the years to improve x-ray methods over the traditional AP and lateral views of the cervical spine. Supplementary views already in use include obliques, lateral flexion and extension, traction, oblique flexion and extension, laminography, myelography, and more recently even cineroentgenography.

Special views are based on cadaver and experimentally produced cervical injuries and have been correlated with extensive clinical studies.[1-4] A 30° caudad angled AP view is recommended to show the apophyseal joints and posterior elements of the lower segments. This gives a symmetrical view of the *normal* apophyseal joints. It is taken in stereo for greater detail (the author has not found this to be entirely necessary). To show C-1, a modified occipito-submental view of the skull is used. For the best shot of Luschka joints an AP view angled 15° cephalad has been suggested. There are further adjuncts. First, the use of 0.3 mm. focal spot tube gives better diagnostic films. This is particularly true of the occipito-submental view of C-1 where the part is necessarily some

*Adapted from Gay and Abbott; *J.A.M.A.*, 152: 1698,1953.

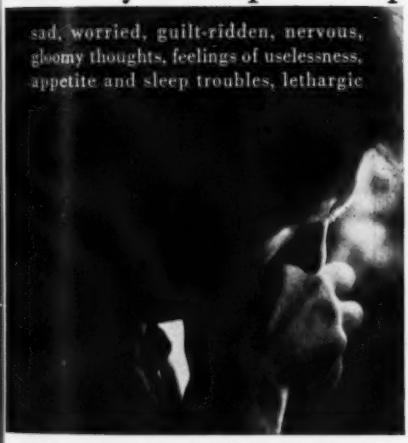
1. Abel, M. S., Moderately Severe Whiplash Injuries of the Cervical Spine and Their Radiological Diagnosis. Read at Eighth Congress of Radiology, Mexico City, 1956.
2. Ibid, Clinical Orthopaedics, in press.
3. Abel, M. S., & Wagner, R. F., Moderately Severe Cervical Whiplash Injuries and Their Radiological Diagnosis. Exhibit Orthopaedic Section, A.M.A., New York City, 1957. A.M.A. Scientific Exhibits, 1957, Grune and Stratton, New York.
4. Wagner, R. F., & Abel, M. S., Small Element Lesions of Cervical Spine Due to Trauma, Read at Drake Hotel, Chicago, October 3, 1958; American Association for the Surgery of Trauma.

now...correct depression safely and rapidly in everyday office practice

Nardil™

brand of phenelzine dihydrogen sulfate

restores your depressed patient to purposeful reality



safely

No significant reports of toxicity to liver, kidneys or blood[1-3] in thousands of cases to date.

rapidly

Antidepressant activity within the first few days; complete recovery occurs within 2 to 6 weeks.

correctively

Removes the depression itself, does not merely mask the symptoms as do tranquilizers and sedatives.

Nardil is indicated in the office treatment of all mild to severe depressions; in those related to childbirth, menopause, old age, or those caused by stress situations; when there is a past history of depressed periods, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis.

Dosage: One tablet three times a day
The above dosage should be maintained until remission of symptoms is achieved which may require 2 to 6 weeks. Dosage should then be reduced to a maintenance level of one or two tablets a day.

Supplied: 15 mg. orange-coated tablets, bottles of 100.

References: **1.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System 20*:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* (in press) 1959.

WARNER CHILCOTT
MORRIS PLAINS, N.J.

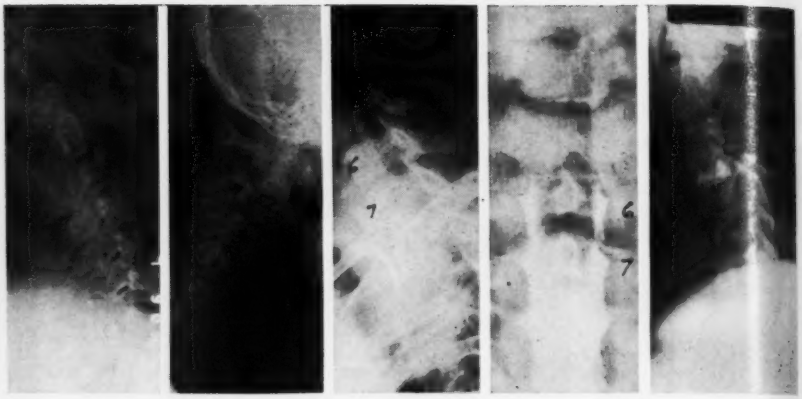


FIGURE 2

Series of roentgenograms of rider motor vehicle traffic accident cervical injuries to illustrate discrepancies between skeletal injuries (or lack of same) and cord damage: 1. No evidence of skeletal injury, with incomplete tetraplegia and recovery. 2. Marked injury at C-2 with no cord damage. 3. No skeletal injury with complete tetraplegia and no recovery. 4. Obstruction shown by myelography in case 3. 5. Fracture dislocation with tetraplegia making for slow recovery after laminectomy and skull traction.

distance from the film. Here a short-tube object distance is used for differential magnification and separation of superimposed structures.

Findings in a series of 100 cases have recently been reported. In order of frequency the patients had:[4]

1. Lateral mass (isthmus) fractures of the lower cervical vertebrae, with or without laminar involvement.
2. Fractured transverse process of C-1. (Fig. 3)
3. Rotational subluxations of C-1 with respect to the occiput, which diagnosis is sometimes hard to make when the head is twisted.
4. Luschka joint fractures.

COMMENT

The prevalence of minor to moderate injuries of the cervical elements is evident even among cases examined by the more-or-less routine techniques of competent roentgenologists. Thus, in a series of cases of the author's,[5] a little over one-half did not reveal subluxations, fractures, or dislocations. Among the remainder, over 80 per cent showed minor to moderate injuries of the cervical elements.

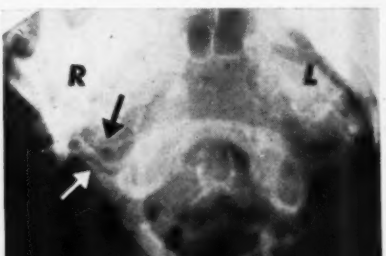


FIGURE 3

Fracture of right transverse process at C-1 shown by Abel technique.*

*Supplied by Dr. Abel of San Francisco.

5. Kulowski, J., *Southern M.J.*, 51:367,1958.

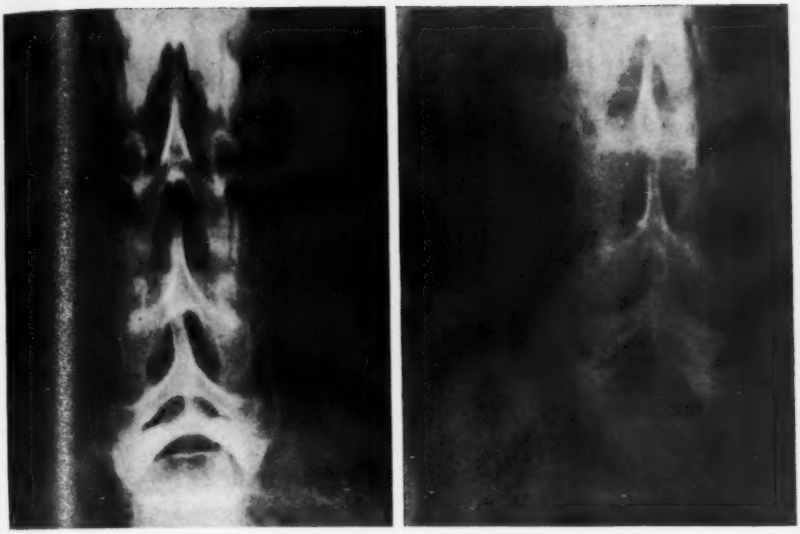


FIGURE 4
Caudad angled view of lumbar spine. Supplied by Dr. Abel.

What is more significant, more of the latter are coming to light since using recently introduced techniques. Undoubtedly some of these had been missed by routine methods in the "negative" x-ray group in the past.

A twin aspect of the problem is that of low-back injuries. Several experimental caudad angled AP views of the lumbar area were made to show the posterior elements better (Fig. 4). The result may be judged by the reader. This area needs further exploration.

DISCUSSION

Despite these advances in radiologic techniques, diagnostic accuracy is hampered by differences of opinion on the x-ray findings and the bizarre nature of some patients' claims. Another pitfall is concomitant arthritis. From the clinical standpoint it is necessary to classify these injuries further, according to whether arthritis is present or not. Was it there prior to the accident? Is it a post-traumatic effect? The answer should not be undertaken lightly. Concomitant arthritis carries a triple threat medicolegal implication: If arthritis existed prior to injury, did it have anything to do with accident causation in the driver-patient? Did the accident aggravate a pre-existing arthritis? Is the arthritis a post-traumatic event?

Evidence has been presented that many of these arthritic manifestations are related to whiplash and other types of accidental injuries (especially the apophyseal arthritis). More specifically, these forms of arthritis are the direct results of small fractures and subluxations of the contiguous anatomical elements. In a series of cases, more than one-half showed concomitant cervical arthritis. This was estimated to have been there prior to accident in about 25 per cent.

Obviously, the more refined diag-

Wigraine
for MIGRAINE

RELIEVES FASTER because Wigraine disintegrates in seconds. Gives prompt effect. No taste or aftertaste.

TREATS ENTIRE SYNDROME: restores cerebral vascular system to normal . . . alleviates nausea, vomiting . . . relieves residual occipital pain.

Wigraine, in tablets and suppositories, supplies:

1 mg. Ergotamine Tartrate
100 mg. Caffeine
0.1 mg. l-Belladonna Alkaloids
130 mg. Acetophenetidin
Tablets—Boxes of 20 and 100
Suppositories—Boxes of 12

Organon Organon Inc. • Orange, N. J.

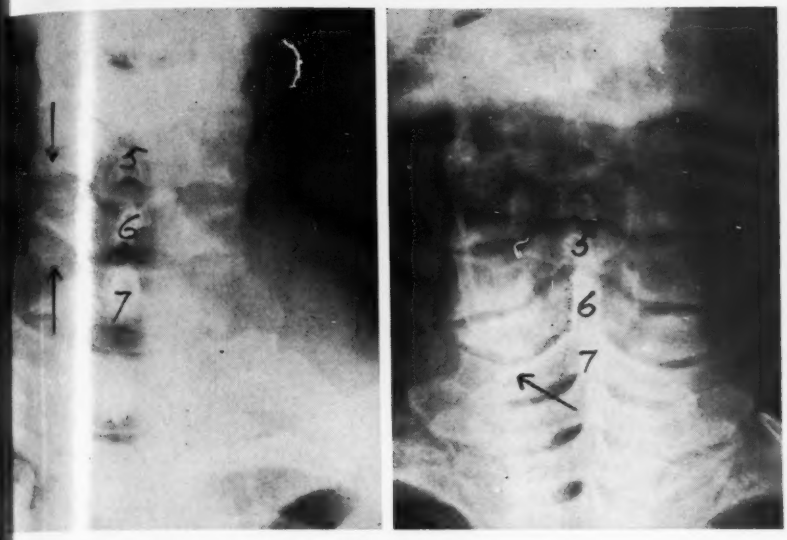


FIGURE 5

Recent case of author's. Injury due to non-collision violence resulting from car lurching forward from a dead stop too fast. 1. Ordinary AP view of cervical spine, apparently negative. 2. Same neck shown by Abel's caudad angled view, showing compression fracture of the lateral mass on right at C-6. Now, a closer look at the left film also shows the fracture deformation at C-6 on right.

ostic findings afforded by the supplementary radiologic views under discussion may be a two-edged sword. On the clinical side, there is no doubt hat treatment can be better adjusted o the individual needs of the patient. Lesser elementary fractures and subuxations, found early, may respond etter to fixative rather than traction ethods. Traction methods seem to o better later on, along with other hysiatric measures.

On the other hand, armed with only light evidences of skeletal deformations (which might better be ignored n the state of our present knowledge), the physician may become verly involved in legalistic complications. In any case, the physician should avoid ever assuming the status of udge, jury or detective in cases involving litigation. This statement can hardly be overstressed.

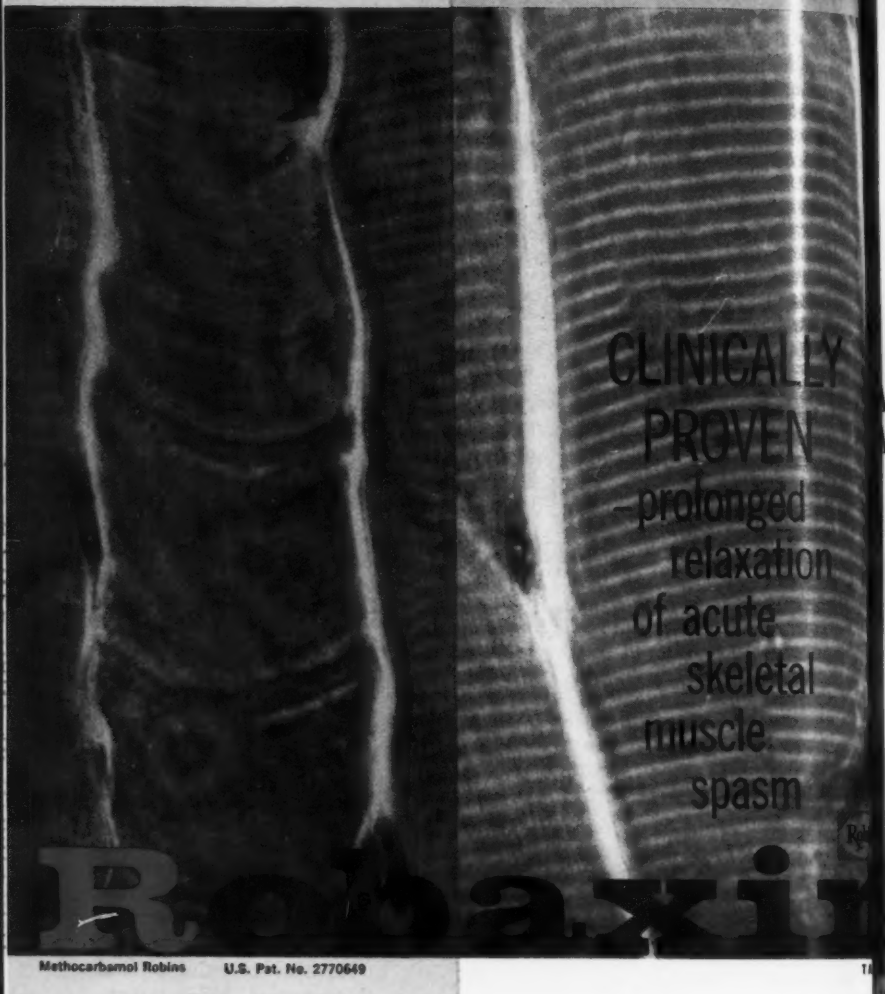
CONCLUDING OPINIONS

Marked differences of opinion exist in regard to the validity of the clinical pictures presented by these patients and the x-ray findings. Some of the arguments on the negative side seem to have resulted from diagnostic frustrations, therapeutic negativism, and medico-legal pressures. From an objective standpoint, a more precise radiological (Fig. 5) and clinical approach has been developed to these cervical injuries—which are so often missed by routine methods of examination alone.

It is to be hoped that a more widespread use of these methods by radiologists will further clarify the interpretation of the findings.◀

Fiber of skeletal muscle in spasm

Fiber of skeletal muscle relaxed (photomicrographs)



Methocarbamol Robins U.S. Pat. No. 2770649

Summary of six published clinical studies:

ROBAXIN BENEFICIAL IN 92.4% OF SKELETAL MUSCLE SPASM CASES

	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
Carpenter[1]	33	26	6	1	–
Forsyth[2]	58	"pronounced" 37	20	–	1
Lewis[3]	38	"good" 25	6	–	7
O'Doherty & Shields[4]	17	"excellent" 14	2	1	0
Park[5]	30	"significant" 27	–	2	1
Plumb[6]	60	"gratifying" 55	–	–	5
TOTALS	236	184 (78.0%)	34 (14.4%)	4	14

- **Highly potent—and long acting.**[1,2,3]
- **Relatively free of adverse side effects.**[1,2,3,5,6]
- **In ordinary dosage, does not reduce muscle strength or reflex activity.**[1]

REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51: 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. L... W. B.: California Med. 90:26, 1959. 4. O'Doherty, D... and Shields, C. D.: J.A.M.A. 167:160, 1958. 5. Park, H... J.A.M.A. 167:168, 1958. 6. Plumb, C. S.: Journal-L... 78:531, 1958.

A. H. ROBINS CO., INC., Richmond 20, Virginia

Ethical Pharmaceuticals of Merit since 1878

ORIGINAL ARTICLE

Analgesic and Hypnotic Effects of an Aminopyrine-Allobarbital Combination

This preparation is especially useful in pain of traumatic origin in patients in whom the usual analgesics had been ineffective

ERWIN E. MAYER, M.D., F.A.C.P., *Baltimore, Maryland*

Many agents for the relief of pain are found on drug counters. Most are actively promoted via television and newspaper with promises of fast relief of pain. The physician must treat a tremendous number of people suffering from various types of pain when these remedies have failed.

Therefore, the doctor must have some oral medicament that combines two important qualities—greater effectiveness and availability only on prescription. A combination of aminopyrine and allobarbital* was ultimately selected. The barbiturate aids in the therapeutic effect and discourages the refilling of the prescription.

Prolonged pain causes an increase in nervous tension. Increased nervousness makes pain less easily endured. A cycle is thus established which often cannot be broken either by a sedative or an analgesic alone, except in extremely large doses. It is in these cases that this combination has proved effective because it acts simultaneously on both the pain and the nervous tension. In addition, relief is usually obtained with relatively small amounts of each constituent.

As team physician for the Baltimore Orioles and the Baltimore

*Cibalgine®, Ciba Pharmaceutical Products, Summit, N. J.

RESULTS OF TREATMENT WITH *CIBALGINE*

INDICATION	NUMBER OF PATIENTS TREATED	NUMBER OF PATIENTS RELIEVED
Dysmenorrhea	27	26
Migraine	32	31
Myalgia	9	9
Osteoarthritis	7	7
Torticollis	5	5
Tension headache	37	37
Post-traumatic pain	5	3
TOTALS	122	118

Colts, where muscle injuries, fractures and sprains have been common occurrences, the author obtained excellent results with the use of this combination for relief of discomfort and pain of injuries and of other origin. The results of the cases most recently seen in our practice are reviewed. While our experience with this preparation goes back over 25 years, a recent study of 122 cases supports the impressions we have obtained over the years.

RESULTS

Its use in dysmenorrhea is exceedingly effective. Two tablets every three to four hours (depending on individual severity) gave relief in 26 of 27 patients treated.

Migraine headache has been found to be a common complaint. There is no drug that will relieve all patients with migraine headache, nor any specific preventive measure or medication. In 32 such patients, the aminopyrine-allobarbital combination proved to be the most useful medication that had been given, with only one patient not responding to therapy. The dosage was two tablets at onset, and two tablets three or four hours subsequently if necessary. It relieved the pain completely, and the acute anxiety so characteristic of this syndrome was simultaneously relieved. No gastric upsets were experienced. These patients had not experienced symptomatic relief with other remedies. The nausea created by ergotamine in some patients was reason enough to avoid its use.

Of five patients given the preparation for post-traumatic pain, two obtained no relief, although one had had no relief from codeine.

OTHER OBSERVATIONS

The preparation has been given to children with measles with good results.

One allergic manifestation was observed in a woman who was given two tablets for headache. She developed urticaria following administration, which was relieved promptly by adrenalin. This patient was also allergic to other drugs including aspirin.

The drug combination does not cause gastric distress as do salicylates. However, in patients where it is not advisable to use salicylates, aminopyrine gives excellent therapeutic results. It can be used in patients allergic to other medications.

The synergistic action of this combination has been noted in a series of studies in which it was reported that

the aminopyrine potentiated the hypnotic effect of the barbiturate so that the combination was superior to the barbiturate alone.[1]

Some have hesitated to utilize products containing aminopyrine because of fear of blood dyscrasia. This apprehension should be largely dispelled by a very thorough study in which it was pointed out that aminopyrine is a uniquely valuable and occasionally life-saving antipyretic which deserves a trial whenever fever is a significant feature of the clinical picture. It may be effective under conditions in which other antipyretics and even the most powerful and specific of the newer drugs fail. The danger of agranulocytosis from its use, although real, has been overemphasized and is no greater than with many other drugs in common use today. Aminopyrine has its place in therapeutics under well controlled clinical conditions and under the supervision of a physician. Only its careless and indiscriminate use is to be condemned.[2]

In a study of many hundreds of cases in which the drug has been used, no evidence of blood dyscrasia has ever been encountered. In this series of 122 cases, blood counts were taken at regular intervals. No marked reduction in circulating leukocytes or other indications of blood dyscrasia were encountered.

SUMMARY

This preparation is especially useful in pain of traumatic origin, such as in muscle injuries, bone fractures and sprains.

In patients in whom the usual analgesics have been ineffective, it gave prompt relief of pain and discomfort of dysmenorrhea, migraine and tension headaches, myalgia, osteoarthritis and tortocollis.

It is an excellent hypnotic. Allergic reaction was noted in only one of the 122 patients studied.

White blood counts were taken on all patients. No case of agranulocytosis was found.◄

1. Nora, P. F., et al., *Illinois M.J.*, 112:161-162,1957.

2. Cardon, L., et al., *Ann. Int. Med.*, 48:1958.

Virilizing Tumor of the Adrenal Gland with Pigmentation and Arterial Hypertension

A girl 2 years of age with a precocious puberty syndrome had heavy, black body hair, the external genital organs were quite developed, acne was present on face and back, muscular power was greater than normal, the voice was deep and harsh, and bone development was that of a child of 6 years. Failure of response to ACTH indicating no hyperplasia of the adrenals, a tumor was sought. X-ray examination revealed a tumor, of grapefruit size, which pressed down the right kidney, which proved to be a corticoadrenal adenoma. After the operation, drop in arterial pressure was prevented by the use of hydrocortisone, cortisone and desoxycorticosterone. The left adrenal gland was reactivated with ACTH. Fifteen months later the child's hair had become blond, the skin smooth and healthy, and the height, weight, and mental development were normal for her age.

Mozziconacci, P., et al., *Semaine hôp. Paris*, 34: 3173-3179,1958.

IN NAUSEA/VOMITING/VERTIG(

ORIGINAL ARTICLE

Treatment of Malignant Tumors of the Nose and Paranasal Sinuses

Seven case histories of tumors of the nose and paranasal sinuses, with details of treatment, are presented

KENNETH D. DEVINE, M.D.,* *Rochester, Minnesota*

In a lifetime of practice most physicians (and this includes many specialists in diseases of the ear, nose and throat) will encounter very few patients who have a malignant tumor of the nasal cavity or of the paranasal sinuses. The patient with a tumor in this region may go an incredibly long time without proper diagnosis. The whole matter may be shrugged off as of slight importance because of the rarity of the tumor and because of a false belief generally prevailing that not much can be done for such patients anyway.

*Section of Plastic Surgery, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TOO MANY COME TOO LATE

The specialist in the treatment of this condition has always pleaded for earlier diagnosis, but statistics continue to show that about half of these patients when seen in treatment centers are considered inoperable. It is true that some are inoperable, not so much because of the extent of the disease as because of the microscopic nature of the tumor. By the time a malignant tumor of the nasal cavity or paranasal sinuses produces symptoms these symptoms are usually late manifestations of far-advanced disease. These symptoms may be presented as bulging or numbness of a

cheek or lip, perforation of the palate, loosening of the teeth or blocking of the nose. These two factors, the microscopic nature of the tumor and the insidious nature of its growth, are the main reasons for poor results of treatment.

LITTLE NEGLECT ON THE PART OF DOCTORS

Very few patients are actually neglected by their physicians. Surprisingly, many patients with far-advanced cancer of this region are responsible for their pitiful condition through their own neglect. Any physician who encounters a patient complaining of recent unilateral nasal obstruction, of "sinusitis," bloody nasal discharge or night-time facial pain should consider the possibility of a malignant tumor. Many of us have heard a patient say that he had asked whether he might not have a cancer, and had been quickly informed that this was impossible, only later to find out that his intuition had been correct.

DIFFERENT METHODS OF TREATMENT

The purpose of this paper is to acquaint readers with the various methods of treating malignant tumors of the nasal cavity and paranasal sinuses by presenting seven cases that illustrate the vagarious nature of tumors in this region. We shall place emphasis on the fact that treatment cannot be stereotyped, that it often requires a team of individuals possessing certain skills, knowledge and tools, and finally that the results can be surprisingly good.

ILLUSTRATIVE CASES

Case 1

A woman of 52 was seen at the Mayo Clinic for the first time on April 15, 1953. She had experienced blockage of her nose on dusty days for 20 years and in the past year the left side had been continuously blocked. On April 13, 1953, several large polyps had been removed from her left nasal cavity, and microscopic examination had showed low-grade, papillary squamous-cell epithelioma. On May 12, 1953, the left nasal cavity and all of the paranasal sinuses on the left were exposed through an external incision which started in the middle of the upper lip, advanced upward to the base of the nose, around the left ala and up the side of the nose, and out into the left eyebrow. The frontal, ethmoidal and maxillary sinuses were exenterated on the left. The sphenoid sinus was not involved. The papillary noninvasive tumor had filled the other sinuses on the left and was easily removed with curettes and rongeurs. The patient was dismissed 10 days later (Fig. 1). There has been no recurrence to date.

Figure 1

Postoperative photograph showing minimal scarring on left side.

This is an example of a tumor of borderline malignancy, and pathologists argue whether or not such a tumor should be called a cancer or a papilloma. There is a history of long-standing blockage of the nose, always unilateral. Usually "polyps" have been removed from time to time for years. Occasionally proptosis occurs. Practically never is there any destruc-

Whatever the indication,*
whatever degree of sedation desired
...a form of Nembutal will meet the need.

(Nothing faster, shorter-acting, safer in barbiturate therapy.)

ABBOTT

NEMBUTAL

(Pentobarbital, Abbott)

*IN THE TREATMENT OF PRE-ECLAMPSIA

cheek or lip, perforation of the palate, loosening of the teeth or blocking of the nose. These two factors, the microscopic nature of the tumor and the insidious nature of its growth, are the main reasons for poor results of treatment.

LITTLE NEGLECT ON THE PART OF DOCTORS

Very few patients are actually neglected by their physicians. Surprisingly, many patients with far-advanced cancer of this region are responsible for their pitiful condition through their own neglect. Any physician who encounters a patient complaining of recent unilateral nasal obstruction, of "sinusitis," bloody nasal discharge or night-time facial pain should consider the possibility of a malignant tumor. Many of us have heard a patient say that he had asked whether he might not have a cancer, and had been quickly informed that this was impossible, only later to find out that his intuition had been correct.

DIFFERENT METHODS OF TREATMENT

The purpose of this paper is to acquaint readers with the various methods of treating malignant tumors of the nasal cavity and paranasal sinuses by presenting seven cases that illustrate the vagarious nature of tumors in this region. We shall place emphasis on the fact that treatment cannot be stereotyped, that it often requires a team of individuals possessing certain skills, knowledge and tools, and finally that the results can be surprisingly good.

ILLUSTRATIVE CASES

Case 1

A woman of 52 was seen at the Mayo Clinic for the first time on April 15, 1953. She had experienced blockage of her nose on dusty days for 20 years and in the past year the left side had been continuously blocked. On April 13, 1953, several large polyps had been removed from her left nasal cavity, and microscopic examination had showed low-grade, papillary squamous-cell epithelioma. On May 12, 1953, the left nasal cavity and all of the paranasal sinuses on the left were exposed through an external incision which started in the middle of the upper lip, advanced upward to the base of the nose, around the left ala and up the side of the nose, and out into the left eyebrow. The frontal, ethmoidal and maxillary sinuses were exenterated on the left. The sphenoid sinus was not involved. The papillary noninvasive tumor had filled the other sinuses on the left and was easily removed with curettes and rongeurs. The patient was dismissed 10 days later (Fig. 1). There has been no recurrence to date.

Figure 1

Postoperative photograph showing minimal scarring on left side.

This is an example of a tumor of borderline malignancy, and pathologists argue whether or not such a tumor should be called a cancer or a papilloma. There is a history of long-standing blockage of the nose, always unilateral. Usually "polyps" have been removed from time to time for years. Occasionally proptosis occurs. Practically never is there any destruc-

Whatever the indication,*
whatever degree of sedation desired
...a form of Nembutal will meet the need.

(Nothing faster, shorter-acting, safer in barbiturate therapy.)

ABBOTT

NEMBUTAL

(Pentobarbital, Abbott)

*IN THE TREATMENT OF PRE-ECLAMPSIA

FIGURE 2a

Postoperative photograph showing patient with resection of upper jaw.

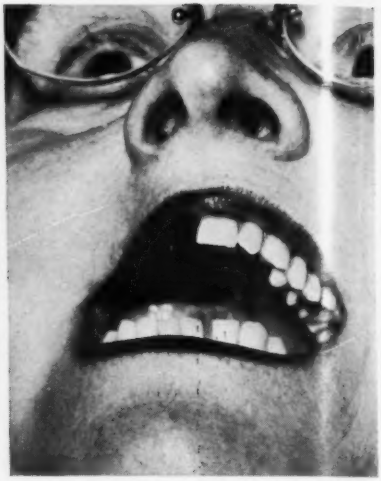


FIGURE 2b

Intra-oral view of same patient showing defect of hard palate.

tion of bone, as shown by x-ray examination of the sinuses. Complete removal is curative, but it usually requires an external incision. Radiation therapy is not satisfactory, and there is some suspicion that such a tumor may undergo a much more malignant change many years after ineffective radiation therapy.

CASE 2

A woman of 51, seen at the Mayo Clinic for the first time on June 30, 1953, had gradual onset of pain on the right side of the face eight weeks previously. The pain was distributed over the zygoma, upper teeth and right side of the nose. X-ray examination of the teeth gave negative results, as did examination of the nose. Roentgenograms of the sinuses showed an opacity of the right antrum. Exploration through a Caldwell incision under the upper lip on June 26, 1953, had disclosed a tumor on the inferolateral wall of the antrum. Biopsy had showed Grade II squamous cell epithelioma. On July 16, 1953, the upper lip was split in the middle and the incision advanced upward around the base of the ala to the inner canthus and outward just below the lashes on the lower lid. The lip and cheek flap was reflected off the face of the maxilla, the upper jaw along with the floor of the orbit was removed with chisels and rongeurs and the cavity lined with a free skin graft. Examination of the specimen showed that the carcinoma involved the lateral and posterior walls of the antrum and that it had extended through the bone laterally. Postoperatively the patient received x-ray therapy. She is alive and well at this time. (Fig. 2a).

This tumor was discovered relatively early, yet it was advanced in the sense that it had already invaded and destroyed the bony wall of the antrum. The proper and early rehabilitation of patients who have the upper jaw resected is dependent upon a well-fitting denture (Fig. 2b) that is specially constructed to close the opening in the hard palate. These patients should be able to eat and speak in a normal manner when wearing their dentures. The use of a skin graft in these cavities speeds up recovery immensely and minimizes deformity from intracavitary scarring and contraction.

CASE 3

A man of 58 had been treated in June, 1956, with a cobalt-60 unit for Grade III squamous cell epithelioma of the left antrum and nasal cavity. He was first seen at the Mayo Clinic on February 7, 1957. Examination revealed palpable cancer along the lower orbital margin and inner canthus just beneath the skin, with elevation of the globe of the left eye. He was in constant pain. Radical resection of the upper jaw was performed on February 12, 1957, and the left orbital contents were sacrificed. When the patient was last seen in June, 1959, he had no evidence of recurrence, was free of pain, and was wearing a satisfactory denture.

The radiologist is an essential member of the treatment team, but rarely does radiation therapy alone produce a cure if the patient harbors a keratinizing squamous cell carcinoma of the nasal cavity or paranasal sinuses. Most of these patients must be treated surgically. There is a trend toward preoperative irradiation followed by operation in 6 to 8 weeks. The question of removing the eye comes up in many of these cases. The former attitude of extreme conservatism in this regard has been changed to one that can be best summed up by saying, it is better to lose an eye than to lose a patient due to recurrence after inadequate treatment brought about by an attempt to save an eye.

CASE 4

A woman of 58 was first seen at the Mayo Clinic on April 18, 1956, with a history of having had epistaxis on the left side over a nine month period. The bleeding had gradually increased in frequency until it occurred every other day. Six weeks previously she had noticed pain in the left side of the face and in the left ear. Her sinuses had been examined with the aid of opaque dye, and a biopsy specimen taken eight days previously showed squamous cell epithelioma, Grade IV. X-ray examination disclosed destruction of the medial wall of the left antrum. Opaque medium could be seen infiltrating the temporal muscles (Fig. 3). On April 24, 1956, the left upper jaw was resected, but it was found at operation that the pterygoid fossa

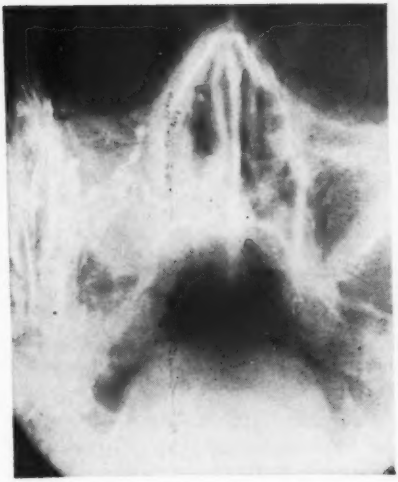


FIGURE 3

Roentgenogram showing infiltration of temporal muscles by opaque medium, indicating defect in antral wall.

was involved. Surgical diathermy (electro-coagulation) was employed, and 14 needles each containing 1 mg. of radium were inserted into the coagulated base. Cobalt-60 therapy was administered postoperatively. The patient is alive and well to date.

This tumor was far advanced and inoperable from a purely surgical viewpoint. Surgical extirpation of cancer in the pterygoid fossa is very difficult. Extension of tumor in this region is better treated by surgical diathermy or interstitial irradiation or both, with supplemental external irradiation. Anyone who undertakes treatment of these tumors should be familiar with all these modalities and they should be available at the time of operation. Frozen section microscopic examination of tissue is very helpful in following extensions of the tumor and determining adequacy of removal.

CASE 5

A man of 42, first seen at the Mayo

Clinic on May 12, 1954, had developed toothache in the right upper jaw 14 months previously. He had noticed that the gum was a little thick. X-ray examination of the sinuses with the aid of radiopaque material and puncture of the antrum were not revealing. One month before, his nose became plugged up and then began to discharge. An abscess in the right upper gum had been drained, and biopsy of a specimen taken through the opening had revealed Grade IV, anaplastic, undifferentiated carcinoma. The right anterior half of the upper jaw was found to be soft and fluctuant, and all of the teeth were loose on this side. Necrotic tumor could be seen in the floor of the right nostril. There was an oro-antral fistula on the right side. The patient received x-ray therapy. He is alive and well and has had no recurrence to date (1958).

Successful treatment of cancer of the antrum is not always dependent upon radical surgical measures. Every case is an individual problem, and treatment must be based on the nature and extent of the growth and on the general condition of the patient. Since the tumor was very anaplastic in this case, radiation therapy seemed to offer more than did surgical therapy. This also is true of tumors of the lymphoma group that occur in this region.

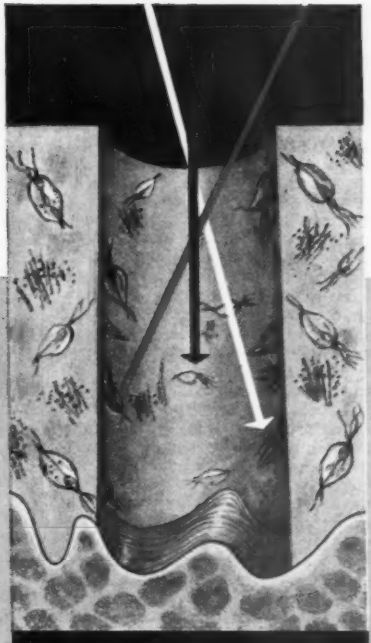
Case 6

A man of 45, first seen on October 25, 1956, gave a history of having had stuffiness of the nose on the left side for six months. Removal of all the tumor through the nostril had been attempted on October 18, 1956, but considerable bleeding had occurred and not all the tumor could be removed. The diagnosis on referral was neuro-esthesioblastoma. Examination disclosed a tumor that filled the upper half of the left nasal cavity and projected into the nasopharynx. The patient received cobalt-60 therapy. Ten months later he returned with recurrence in the left nostril. Again he received cobalt-60 therapy. Four months later he returned with more tumor in the left nostril. He was operated on on May 6, 1958, two years after the onset of symptoms, 18 months after his first course of cobalt-60 therapy, and four months after his second course of cobalt-60 therapy. The lip was split up the middle and the incision advanced around the base of the nose up to the inner canthus and out into the left eyebrow. Removal of the nasal bone and the medial half of the face of the left maxilla permitted easy access to the left nasal cavity. The tumor arose from the olfactory groove along its entire length. Removal of the cribriform plate exposed tumor tissue deep to the dura. A neurosurgeon removed the intradural extension of the tumor which measured 1 by 1 by 3 mm. The cavity was covered with a free skin graft. The patient was dismissed from the hospital in 1 week. There has been no recurrence to date (June, 1959).

Neuro-esthesioblastoma is a rare nasal tumor that only recently has been classified as a distinct entity. It is malignant and seems to occur in two or more varieties: A highly malignant one that spreads widely through the body, and a rather slowly growing one that is less malignant. It is difficult to know by microscopic examination alone which variety the patient may be harboring. It has been reported that these tumors are radiosensitive. Consequently, cobalt-60 therapy was chosen for this patient, although none of these tumors has been cured by radiation therapy alone, in our experience.

Exposure is the *sine qua non* of cancer surgery and this is especially true in the surgical treatment of malignant tumors of the nasal cavity. Exposure permitted visualization of the intradural extension of the tumor in this case, and fortunately immediate help was available from the neurosurgeons. Skin grafts can be laid upon the dura and brain without any fear that they may not take. They permit early sealing off of the cranial cavity from the nasal cavity, and help to guard against cerebrospinal rhinorrhea, meningitis and brain abscess.

This patient was not treated by resection of the upper jaw, or by radical resection of the upper jaw with the orbital contents. Doing these operations routinely and blindly as set



Vaginal submucosa with mucopurulent layer.

Superior control of Leukorrhea

LYCINATE

SEEKS OUT, EXPOSES *and* **DESTROYS** *the exudate-protected Trichomonad and Monilia*

Lycinate accomplishes the two factors essential to successful therapy in Leukorrhea:

first—**Penetrates the mucopurulent barrier surrounding the hidden pathogens.**

second—**Effectively kills these offending pathogens.**

Lycinate, through extremely effective mucolytic action, penetrates, exposes and then destroys these organisms by both chemotherapeutic and lysing actions.

Sustained effectiveness is insured by 'round-the-clock tablet disintegration.

Each buffered Lycinate tablet contains as active ingredients:

Diiodohydroxyquin	100 mg.
Sodium lauryl sulfate	5 mg.
Dioctyl sodium sulfosuccinate	5 mg.
Dextrose, anhydrous	650 mg.

dosage: 1 or 2 vaginal tablets inserted simultaneously once daily.

supplied: Boxes of 50 with applicator.

LLOYD BROTHERS, INC. CINCINNATI 3, OHIO

procedures for cancer of the nasal cavity and paranasal sinuses will mutilate many patients unnecessarily. The operation must fit the disease.

CASE 7

A woman of 39, first seen on November 30, 1953, had had blockage of her right nostril for four months before she had undergone polypectomy in October, 1951. Examination of the tissue removed had shown fibrosarcoma, and later the same month a "more radical bone resection" had been done through the nostril. She began to have constant burning in back of both eyes and occasional sharp jabbing pains in back of the right eye shortly after operation. Twenty-one months after her operation she had blurring of vision in the right eye which advanced until the eye became blind. Twenty-three months after her operation, the right eyeball had begun to protrude and the protrusion had continued to increase. Examination on admission to the clinic showed proptosis (Fig. 4). December 5, 1953, the complete orbital contents were exenterated back to the optic foramen. The cribriform plate and the medial wall of the antrum were removed. The roof of the antrum (floor of the orbit) had been destroyed by the tumor. No ethmoid cells remained in the nose—since they had been removed at the previous operation. Postoperatively the cavity was irradiated intensively with 50 mg. tubes of radium packed into the cavity, and supplemental x-ray therapy was used. The pathologic diagnosis was Grade IV rhabdomyosarcoma. The patient is alive and well at the time of this writing (1959).

This tumor probably was primary in the orbit, and only secondarily involved the nasal cavity by eroding through the lamina papyracea and entering the nose in the ethmoid area to cause nasal obstruction. The case demonstrates that vigorous, combined radical surgical treatment and intensive radiation therapy offer some hope for an occasional so-called hopeless case. The physician who sees cases of this kind is sorely tried if he earnestly attempts to do what seems to be the best for the patient. On the one hand he tries not to become too enthusiastic and not to be carried away by the ability to "get away" with "big operations" for far-advanced disease, and on the other hand he does not want to be too timid and conservative and refuse to operate on a patient who might get well. The decision regarding whether or not to operate is reached by mutual understanding between patient and physician, and often the reason for the decision may not be apparent to others, nor communicable to others. Frequently there are no "logical reasons"—only a "hunch" or a feeling. This certainly is not a very scientific approach, but nevertheless is one that every physician must use in many cases if he practices the art of medicine.◀

FIGURE 4

Photograph showing proptosis of eyeball.

ORIGINAL ARTICLE

Are You Using Oxytocin Properly?

Disregard for contraindications and proper dosage of oxytocin may result in maternal and fetal catastrophes

D. FRANK KALTREIDER, M.D.,* *Baltimore, Maryland*

The unanimous opinion of The Maternal Mortality Committee was that the death was preventable. The cause of death? Rupture of the uterus. The etiology of the rupture? The injudicious use of an oxytocic during labor. The same conclusions were reached by The Committee on two deaths while discussing eight.

It is unfortunate that so excellent an adjunctive therapeutic agent as oxytocin[1,2] is the cause of so many unnecessary hysterectomies and deaths. The agent itself is not to blame, but rather its indiscriminate use in conditions where it is contraindicated.

*Department of Obstetrics and Gynecology, University of Maryland School of Medicine.

1. *Pitocin*®, Parke Davis & Co., Detroit.
2. *Syntocinon*®, Sandoz Pharmaceuticals, Hanover, N. J.

CONTRAINDICATIONS

Parity Over Four

Uterine ruptures caused by oxytocin appear to have a higher than expected incidence with parities over four, although this has not been corroborated. The uterine muscle in a patient of higher parity apparently has poorer tone than that in a patient of lower parity. Moreover, it will often react explosively to oxytocin. If the uterine muscle has been compromised by a previous pregnancy where an incomplete laceration of the lower uterine segment was

sustained, the scar can and does rupture explosively during labor.

Age Over 35

Even the woman over 35 of low parity seems to have poorer uterine muscle tone than a younger woman. Placental insufficiency is also associated with pregnancy in the elderly primigravida, and any further reduction of efficiency by prolonged contractions may handicap the fetus to the extent of lethal or sublethal anoxia.

Abnormal Presentations

Stimulation of labor is contraindicated in the transverse lie, since the fetus cannot be delivered vaginally; the brow presentation, unless associated with prematurity, since attempts to relieve dystocia by overcoming the disproportion between fetus and pelvis with increased uterine contractions inevitably result in uterine rupture and fetal death; and the face presentation, when oriented posteriorly or associated with a small pelvis, for the same reason as stated for the brow presentation.

Without iatrogenic aid the compound presentation carries a high perinatal loss, the risk of which may be increased by the stimulation of labor. Investigators employing oxytocin intravenously generally suggest that it should not be used in breech persentations, and if there is any further complication, particularly a small pelvis, the author agrees. However, if the problem is one of inertia alone, the patient can be cautiously stimulated with safety.

Excessively Large Infant

Although accurate estimation of fetal size is difficult, a valid estimate may be reached by averaging estimates of several trained examiners. Our experience has shown this to be a reliable method.

Contracted Pelvis

Abnormal presentation, large infant, and contracted pelvis are so intimately involved they could be grouped under the heading "feto-pelvic disproportion." Compatible relationships between all these factors must exist if risk to infant or mother during oxytocic stimulation is to be kept minimal.

X-ray pelvimetry is a requisite for oxytocin stimulation, since irreparable damage to the infant's brain can and does result from attempting to overcome disproportion by forcing the descent of the vertex. The damage accrues from molding and hypertonic uterine contractions.

One of the most common indications for the use of oxytocin is primary uterine inertia. However, it is imperative that the inertia be proven not a result of abnormal feto-pelvic relationship or some obstruction of the pelvic canal. For this reason careful re-determination of fetal size and presentation, and of pelvic capacity is necessary in order to prevent disaster to infant and mother.

Previous Uterine Surgery

Previous cesarean section or myomectomy, plastic repairs of the cervix, unification of the bicornuate uterus and other similar repairs are also contraindications to oxytocin.

Infection

If the mother has an infection her oxygen requirements increase, thereby reducing the amount available for the fetus. If the infection should in-

n Coronary
nsufficiency . . .

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.

Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

IMPROVED CORONARY BLOOD SUPPLY with Miltrate increases his exercise tolerance.

Miltrate*

Miltown® (*meprobamate*) + PETN

Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Supplied: Bottles of 50 tablets.
Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

WALLACE LABORATORIES • *New Brunswick, N. J.*

CML-9181-59 *TRADE-MARK

volve the infant, the situation is compounded, since the infant then needs more oxygen for its own increased metabolism.

States Compromising the Fetus

Any obstetrical or medical complication compromising the infant's oxygen supply should contraindicate the use of a uterine muscle stimulant. Known causes of fetal distress such as heart disease, postmaturity, prematurity, and maternal anemias are examples. There are exceptions to this rule, as when it is imperative to induce labor because of maternal complications. In such a situation maternal welfare should have priority.

The fetus should be considered as well as the mother when oxytocin is used. It is common during uterine contractions to observe evidence of transient fetal anoxia while between contractions there is evidence of recovery. When such distress occurs early in labor, increasing anoxia is frequently evidenced as labor progresses, since uterine contractions become stronger and last longer while the diastolic phase is shortened. If uterine contractions are stimulated artificially, a similar pattern may follow possibly resulting in sublethal and even lethal, fetal anoxia.

Normal Labor

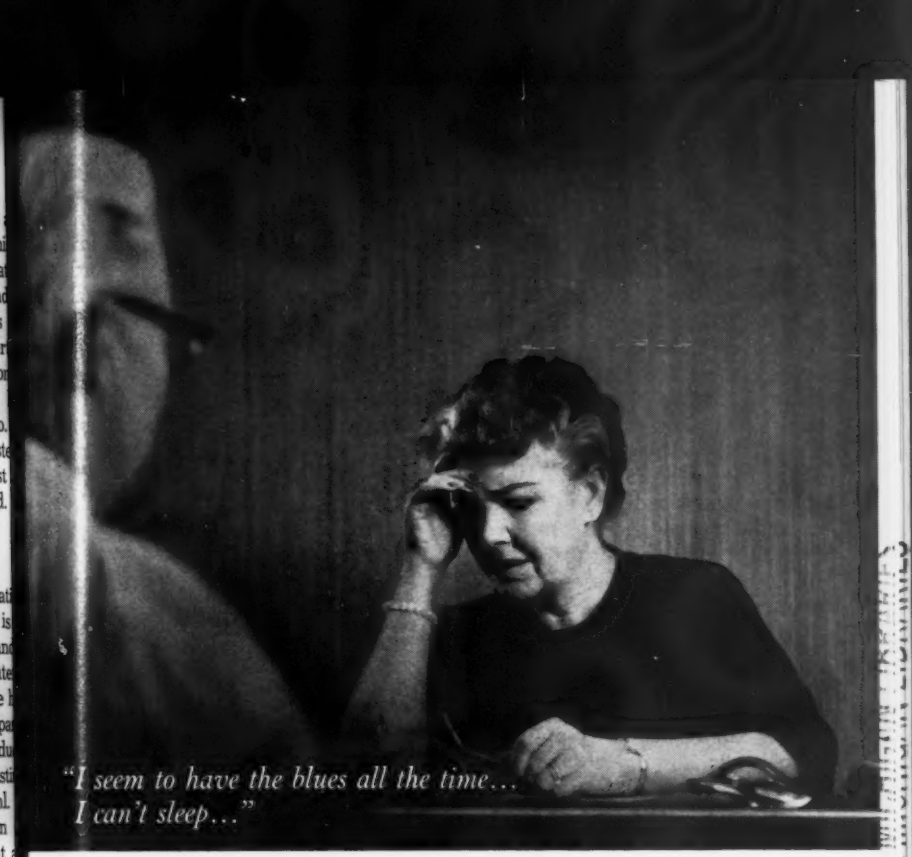
Normal uterine contractions require no stimulation. It follows that in a labor proceeding normally, the use of oxytocin is contraindicated.

Labor is now frequently induced for convenience, its protagonists insisting that there are no dangers. This may be so in selected cases since the human becomes easily accommodated to specific conditions. However, after acclimatation by repetition the specific indications become br adened less care is maintained with fam procedures, until some complica arises. This applies to elective in tion of labor. The prerequisites success—engagement of the ver 2-3 cm. dilation with proportio effacement of the cervix, and parity—are no longer adhered to. gain in convenience for the obst cian can justify even the least crease in risk to mother or child.

DOSAGE

Errors in judgment of indicat are frequent. Just as frequent is adequate attention to dosage an observation of the contracting ute A para 4 of 33 in labor must be h dled with more caution than a pa of 18 whose labor is being indu The former can probably be sti lated satisfactorily with 0.25 ml. ampule, 2.5 I.U.) of oxytocin 1,000 ml. of isotonic glucose at trated rate, intravenously. In the ter this dosage would more li barely increase Braxton-Hicks tractions. A sensible approach titrating procedure. Starting wi dilute solution, the rate of drip be cautiously accelerated or the centration may be gradually creased. The solution should b luted when the patient approach contraindication, either by her s or complications. When the pati status is such that the least da exists, a satisfactory dosage is 0.5 in 500 ml. of isotonic glucose a rate of 12-15 drops per minute. H ever, individualization is inescap

A few physicians are using th tramuscular route for administra This seems to me unsafe. On tient may absorb the drug rapidly other slowly. The intravenous



in the depressed, unhappy patient

PROMPTLY IMPROVES MOOD

without excitation

- **Acts fast to relieve depression and its common symptoms:** sadness, crying, anorexia, listlessness, irritability, rumination, and insomnia.
- **Restores normal sleep**—without hang-over or depressive aftereffects. Usually eliminates need for sedative-hypnotics.

Composition: Each light-pink, scored tablet contains 1 mg. benactyzine HCl and 400 mg. meprobamate.

Dosage: 1 tablet q.i.d.

for depression

▲Deprol▲†

†TRADE-MARK

WALLACE LABORATORIES, *New Brunswick, N. J.*

CD-9188

leaves no doubt on this score. With this method the only variable is the sensitivity of the uterine muscle to any one unit of oxytocin. When one considers that 0.5 ml. of oxytocin in 500 ml. of fluid given at the rate of 15 drops per minute deposits only 0.005 units of oxytocin intravenously per minute, the extreme potency of the drug can be better comprehended. There cannot be too many molecules entering the blood stream at any one minute, yet vigorous contractions can be produced with this minute amount. Why risk increasing the dosage several times by variable absorption using the intramuscular route?

An abnormal contraction can occur within the first few seconds of administration or at any later time during administration. For this reason constant attention is necessary to observe abnormalities of contraction as soon as they occur. Although the multipara whose contractions are two minutes apart, lasting 50 to 60 seconds with no change in cervical dilation, is often considered in no danger, this situation is just as conducive to fetal anoxia and uterine rupture as some of the previously mentioned more obvious conditions. Uterine contractions in labor must approach the norm and not exceed it if the result is to be considered successful. This entails normal uterine contractions as to intensity and duration, and the tone between contractions should be normal. Cervical dilation should proceed at a rate compatible with the type of contractions involved. Anything more than this may spell trouble, and the solution should be cut off immediately since the chances are that no further drug is needed. If the recommendation to administer oxytocin until the labor is completed is followed without regard to the type and progress of labor, there could be occasional disaster.

SUMMARY

Oxytocin is useful as an aid in emptying the uterus in inevitable and incomplete abortion, for induction of labor, for modification of the uterine dystonias or dysrhythmias, and for control of hemorrhage during the third and fourth stages of labor. The wide usage has occasionally resulted in fetal and maternal catastrophes. When oxytocin is used the safety of mother and fetus can be guarded only by adherence to precise indications, meticulous avoidance of contraindications, cautious consideration of dosage, and unending observation of the condition of both patients.◀

Fat Embolism in Chronic Alcoholism

Morning sputum samples from 51 patients with alcoholic psychosis were examined for fat droplets, which were found in 48 of them. Three patients with sputums showing no fat globules had little more than "hangovers." It is concluded that fat embolism is of common occurrence in chronic alcoholics. It is recognized as a major factor in the causation of alcoholic psychosis and may be the cause of death in some such cases. Repeated fat embolism may be the basis of few or many of the changes found at necropsy in the brains of chronic alcoholics.

Lynch, M. J. G., et al., *A.M.A. Arch. Path.*, 67:68-80,1959.

ORIGINAL ARTICLE

Hemangiomas in Infants

These tumors should be eradicated at infancy, preferably with radium irradiation, since they may grow large enough to result in permanent disfiguration

J. ERNEST BREED, M.D., *Chicago, Illinois*

Hemangiomas in infants are common, yet much confusion exists as to their proper care. The fact that many will remain stationary or disappear in time causes some physicians to suggest no therapy. The rapidly enlarging growth should have special attention because it may produce lifelong disfiguration or destruction of essential tissues.

COMPOSITION

Hemangiomas are tumors composed of blood vessels and fibrous tissue. The vessels may be capillaries, veins or arteries, varying in size from capillaries to large blood spaces. The fibrous tissue may range from a small amount of supporting tissue to a state in which it comprises the major portion of the tumor. The mass may be fed by a single vessel or by many vessels.

CLASSIFICATION

Classification is based upon the composition, shape, size and color of the growth. The term hemangioma simplex includes those composed of capillaries or very small arterioles or venules. Port-wine stains and nevus flammeous are in this group. The term cavernous hemangioma describes those in which the vascular channels are widely dilated and the connective tissue is sparse. Spider nevi are composed of tiny vessels radiating from a single central artery.

DISTRIBUTION AND MODE OF GROWTH

These tumors may appear in any part of the body. The deep seated growths are difficult to diagnose because they seldom give symptoms. Hemangiomas of the skin or subcutaneous tissues are accessible, may be diagnosed early, and present the problem under discussion in the paper. They are either present at birth or appear shortly after. Some grow only with the child. Some grow slowly for a time, then remain stationary or spontaneously recede. Others grow steadily until they obtain great size, infiltrating and destroying the adjacent tissues and in time perhaps producing a discharging and bleeding ulcer. At times they become so large that they endanger the life of the child. There is no way of knowing in advance which hemangiomas will continue to enlarge. Often an unfortunate policy of wishful expectancy is followed until the tumor has obtained such size that permanent disfiguration is inevitable.

TREATMENT

There is considerable diversity of opinion as to when treatment should be started and what treatment should be administered. Some believe that all lesions should receive definitive treatment as soon as possible. Some recommend that only those that are enlarging should be attacked. Still others start treatment only after the hemangioma has proved its destructive nature.

Because of its simplicity, freezing with carbon dioxide snow is widely used. This method is painful, destroys only the superficial parts of the growth and is usually followed by a scar.

Injection of the mass with sclerosing solutions may produce irregular shrinkage of the mass and usually leaves a blotchy skin. It also is quite painful.

Small spider nevi fed by a single central vessel will disappear if the vessel is destroyed by fulguration or with the galvanic needle.

Surgical removal is practiced by some. Because the incision is made as close to the mass as possible, recurrence is common from the peripheral portions of the tumor. Many hemangiomas are on the face or other exposed portions of the body, so the scarring from surgical removal is sometimes worse than the growth.

Most commonly, some form of irradiation is employed. A few very superficial growths have been treated with strontium^{90} with good results. This element emanates only beta rays of little energy, making it useless in growths of more than a few millimeters in thickness.

X-rays are used by many. Although I have seen no report on the use of the contact x-ray tube, I believe this agent would be quite effective in lesions over 1 cm. in thickness. The target of the tube should be as close to the surface of the growth as possible. Conventional x-ray from a distance of 10 to 50 cm. from the lesion delivers a high percentage of the dose to the deeper structures, and may permanently injure sensitive epiphyseal lines or other vital tissues often lying beneath the growth.

RADIUM THERAPY

Radium gives off two types of rays: beta rays and gamma rays. Beta rays are composed of electrons thrown out of the radium nucleus with varying amounts of energy. Being particles of matter, even those with an energy of

3 m.e.v. will penetrate tissue no deeper than 1 cm. They are ideal in the treatment of hemangiomas 6 mm. or less in thickness. The quantity of radium in the applicator is small, so that few of the penetrating gamma rays are present.

The beta rays vary in energy from a few thousand to 3 million m.e.v. The weaker (soft) rays are absorbed in the first 2 mm. of tissue and must be screened off with 1/10 mm. of lead or its equivalent. The more energetic rays (hard) will be effective to a depth of 8 mm. I use a one-quarter strength beta-ray radium applicator screened with 1/10 mm. of lead and 2 mm. of rubber to treat superficial hemangiomas of not over 6 mm. in thickness.

Thick tumors or subcutaneous tumors must be treated with gamma rays. The element is placed close to the surface of the tumor. Structures beneath the growth receive only a fraction of the tumor dose, in accordance with the inverse square law. The selected distance from the applicator to the skin may be obtained by strapping a block of rubber or wood of the desired thickness to the surface of the tumor. The radium is applied around the periphery of the growth according to the technic of Paterson and Parker, permitting uniform irradiation.

There is a natural tendency for the normal tissues to inhibit the growth of the angiomas antagonistic to the inherent tendency of the growth to enlarge. Radium therapy discourages the growth of the tumor, probably through injury to the radio-sensitive blood vessel endothelium, and perhaps accentuates the defenses of the body by slight reaction in the tumor bed. The total dosage administered is a small fraction of that normally given in the treatment of cancer.

The course of treatment is spread over three or four weeks, a small dose being given every other day. No two hemangiomas react alike, so the sensitivity of the growth can be learned only through observing the tumor as it shrinks. Treatment is continued until the mass has shrunk to half of its former size or until 1,000 gamma r have been given to the skin surface. If tanning or redness of the adjacent skin appears, treatment is discontinued.

Resolution of a tumor usually is slow. Many weeks or even months may pass before all evidence of the growth has disappeared. Nothing more is done as long as shrinkage continues. If resolution stops or if regrowth occurs, a second course of treatment is given. About 2 per cent of all my patients required retreatment.

EARLIEST INFANCY THE TIME TO BEGIN FOR SOME TUMORS

Treatment of an enlarging hemangioma should be started in earliest infancy. It is true that some of the tumors which might otherwise go away spontaneously will be treated. Treatment nevertheless is well worthwhile because the hemangiomas are not permitted to grow large enough to produce permanent scarring.

The greatest value of treatment lies in the destruction of the tumors that otherwise would grow to large size. The greater the delay in starting treatment, the larger and more radioresistant the lesions become. Even the resistant port-wine stains, in some patients, may be lightened if treated very early.

In the past 25 years I have treated more than 1,000 hemangiomas in in-

attle

n the office

often lost in the stomach

Your ulcer and spastic-gut patients, who reflect their emotions in their stomachs, will more easily maintain "g.i. equilibrium" with the help of 'Combid' *Spansule* capsules.

'Combid' reduces secretion
spasm
nausea and vomiting
anxiety, tension and stress

for 10 to 12 hours after just one dose.

Each capsule contains Compazine‡, 10 mg.; and Darbid§, S.K.F.'s *inherently long-acting* anticholinergic, 5 mg.

Combid* Spansule† b.i.d.

Smith Kline & French Laboratories

★T.M. Reg. U.S. Pat. Off. †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.
‡T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.

fants. In a careful follow-up of most of these patients no ill effects have been observed, either as scar from irradiation or damage to deeper structures. As a rule no residual evidence of the lesion remains, unless ulceration of the tumor had already occurred before treatment was started.

I have used cobalt^{60} as a source of gamma rays in some large growths. It has no advantage over radium. It emits no beta rays, therefore cannot be used with beta ray technic.

SUMMARY

Hemangiomas are tumors, the cells of which tend to form blood vessels. Appearing at birth or shortly after, they may remain stationary, or grow for a time and then recede, or grow rapidly and destroy the adjacent normal structures. Seldom do they become malignant.

A spider nevus, fed by a single central vessel, is best treated by coagulation of that vessel. There is much diversity of opinion on the treatment of other hemangiomas.

Beta-ray therapy from radium for superficial tumors, and gamma ray treatment from radium or cobalt^{60} for the deeper lying growths, have proved effective in most cases. Among 1,000 of my infant patients with hemangiomas, fewer than 2 per cent needed further treatment◀

CLINICAL NOTE

The Use of Triclobisonium Chloride in Dermatoses

The compound was effective either alone or with hydrocortisone in a variety of common dermatoses

LEONARD D. GRAYSON, M.D.,* and
HILLIARD M. SHAIR, M.D.,* *Quincy, Illinois*

In-vitro studies have revealed that triclobisonium chloride,† a bisquaternary compound, has high activity against five strains of streptococci (higher than oleandomycin and furacin but lower than penicillin). Eight staphylococcal strains were studied and it was found that seven were resistant to furacin, six to penicillin, five to oleandomycin, and none to triclobisonium chloride. The effectiveness against E. coli was somewhat erratic. Antifungal activity revealed effectiveness against Trichophyton mentagrophytes and Microsporum canosum. Triclobisonium chloride also seems to have an antitrichomonal activity.

In pre-clinical trials[1,2] skin reactions were found in less than 2 per cent of all patients tested. It has been recommended for use in impetigo, furunculosis, tinea capitis, seborrheic dermatitis, otitis externa, sinusitis, rhinitis, cystitis, vaginitis, burns, irrigation of wounds, & conjuctivitis.

Triclobisonium chloride 0.1% ointment (Carbowax base) and Triclo-

* Department of Dermatology, Physicians and Surgeons Clinic, Quincy, Illinois.
† *Triburon®*, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

1. Edelson, E., et al., Clinical Appraisal of a New Topical Quaternary Compound (RO5-0810---1), Presented before the Sixth Annual Symposium on Antibiotics, Washington, D.C., Oct. 15-17, 1958.
2. Robinson, R. C. V., & Harmon, L. E., Local Application of Triclobisonium Chloride; A Quaternary Ammonium Compound in Pyodermas, Presented before the Sixth Annual Symposium on Antibiotics, Washington, D.C., Oct. 15-17, 1958.

WHEN DIET ALONE DOESN'T DO IT...CONSIDER DIABINESE® FIRST

brand of chlorpropamide

The specific pharmacologic properties of DIABINESE—high activity, freedom from metabolic degradation, and gradual excretion—permit (1) prompt lowering of elevated blood sugar levels *without a "loading" dose*, and (2) smooth, sustained maintenance "devoid of...marked blood sugar fluctuations"[1] on convenient, lower-cost, once-a-day dosage. This is the consensus of extensive clinical literature.[1-11] Widespread use of DIABINESE since its introduction has confirmed the low incidence of side effects reported by the original investigators.

Thus, DIABINESE merits *first* consideration for any diabetic presently receiving or potentially better managed with oral therapy—including many diabetics for whom previous oral agents have proved ineffective.

Supplied: Tablets, white, scored 250 mg., bottles of 60 and 250; 100 mg., bottles of 100.

tablets / once-a-day dosage

for smoother, lower-cost oral antidiabetic control

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES, Brooklyn 6, New York
Division. Chas. Pfizer & Co., Inc

1. Greenhouse, B.: Ann. New York Acad. Sc. 74:643, 1959. 2. Dobson, H. al.: Ibid., p. 940. 3. Forsham, P. H.; Magid, G. J., and Dorosin, D. E.: p. 672. 4. Beaser, S. B.: Ibid., p. 701; New England J. Med. 259: 1958. 5. Bloch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74: 1959. 6. O'Driscoll, B. J.: Lancet 2:749, 1958. 7. Hadley, W. B.; Kha adurian, A., and Marble, A.: Ann. New York Acad. Sc. 74:621, 1959. 8. D can, G. G.; Schless, G. L., and Demeshkieh, M. M. A.: Ibid., p. 717. 9. H delsman, M. B.; Levitt, L., and Calabretta, M. F.: Ibid., p. 632. 10. H A. G., and Abelove, W. A.: Ibid., p. 845. 11. Drey, N. W., et al.: Ibid., p. 9

TABLE 1

RESULTS OF TREATMENT WITH *TRIBURON* OINTMENT

DIAGNOSIS	Excellent	Good	Fair	No Effect	Side Effect	Number Patients
Pyoderma	4	3	0	2	1	9
Hidradenitis suppurativa	1	1	1	0	0	3
Hand eczema	2	1	0	0	0	3
Infected hemangioma	1	0	0	1	0	2
Infected sebaceous cyst	1	0	0	0	0	1
Infected trophic ulcer	1	0	0	0	0	1
Dermatitis—Legs	0	0	0	1	1	1
Pemphigus with Infected Lesion	1	0	0	0	0	1
Acne	0	0	0	1	0	1
Infection Nasal Vibrissae	0	1	0	0	0	1
Seborrheic dermatitis	0	1	0	0	1	1
Pruritus ani	1	0	0	0	0	1
Post-Radiation Necrosis	0	1	0	0	0	1
Post-Surgical Reaction	0	0	1	0	0	1
TOTALS	12	8	2	5	3	27

TABLE 2

RESULTS OF TREATMENT WITH *TRIBURON* WITH HYDROCORTISONE

DIAGNOSIS	Excellent	Good	Fair	No Effect	Side Effect	Number Patients
Pyoderma	2	1	0	0	0	3
Atopic Dermatitis	2	0	0	1	0	3
Eczema	3	2	1	0	0	6
Lichen simplex chronicus	0	0	0	1	0	1
Tinea profunda	0	0	0	1	0	1
TOTALS	7	3	1	3	0	14

bisonium chloride with hydrocortisone ½% ointment were used in this clinical evaluation.

Table 1 (use of Triclobisonium chloride ointment) reveals that in those skin diseases in which infection played a major part, there were nine excellent and five good results out of 18 cases. In nine cases in which infection played either a small or no part, there were three excellent and three good therapeutic results. It is interesting to note that in hand eczema with no obvious infection the results were very good. In one case of dermatitis of the legs in which the medication was not beneficial, there seemed to be irritation after using it for some time. In the case of seborrheic dermatitis with good results the patient had a burning sensation whenever the medication was applied. In one case with a carbuncle Triburon burned every time the patient applied it. Table 2 (triclobisonium chloride and hydrocortisone) reveals about the same effectiveness as found with Triclobisonium chloride alone. Although there were no complaints of burning or irritation (this could be explained by the smaller number of cases), there is no significant therapeutic difference between the two preparations.◀

PARTICULARLY

for the "OB" patient who requires antibiotic therapy

COSA-TETRASTATIN®

glucosamine-potentiated tetracycline with nystatin

Because women during pregnancy are particularly prone to secondary fungal infection, they benefit from the extra protection of nystatin.

Cosa-Tetracyn® (glucosamine-potentiated tetracycline) provides peak levels of antibiotic activity against a broad range of susceptible organisms.

Nystatin provides specific protection against overgrowth of Candida albicans.

COSA-TETRASTATIN *provides tetracycline effectiveness with minimum risk of moniliasis.*

Supplied:

Capsules *(pink & black)* 250 mg. Cosa-Tetracyn plus 250,000 u. nystatin

Oral Suspension *(orange-pineapple flavor)*, 2 oz. bottle, each tsp. (5 cc.) contains 125 mg. Cosa-Tetracyn plus 125,000 u. nystatin

A Professional Information Booklet providing complete details on Cosa-Tetrastatin is available on request.

Pfizer™ *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

An Internist Discusses Gastric Ulcer

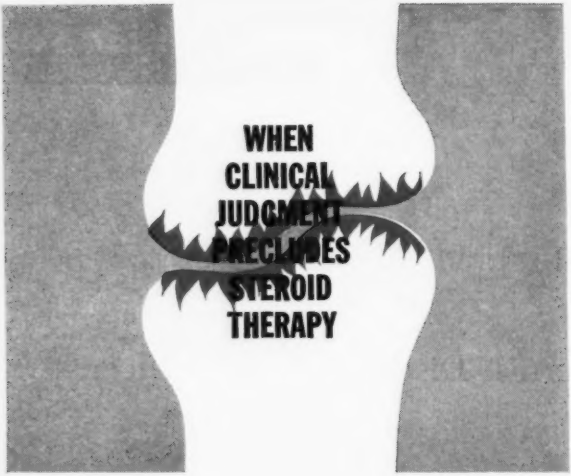
If the history and laboratory findings show the ulcer to be benign, a strict medical regimen is adopted

THOMAS A. JOHNSON, M.D., *Philadelphia, Pennsylvania*

With full realization of the risk involved to the patient, I believe that it is the duty of the internist to make every effort to exclude from surgery any gastric ulcer in which the preponderance of evidence favors a benign lesion. There will be mistakes, but we must balance those mistakes against the not unimportant considerations of mortality and morbidity of gastric surgery in the average hospital. The morbidity of gastric surgery at the hands of the most experienced surgeons requires comment. An inevitable group of cases with dumping syndrome, postgastrectomy steatorrhea, iron deficiency anemia, and various other deficiency states, all of which may be condoned in the presence of necessary surgery, imposes an intolerable penalty upon the patient on whom unnecessary surgery is performed.

All realize that the differential diagnosis between benign and malignant gastric ulcer represents an educated guess. The major decision is to exclude early malignancy, in which surgical results are best. If the gastric ulcer is 4 cm. in diameter, the decision for surgery is not very difficult. A benign lesion of that size usually will not heal satisfactorily, and may require surgery. A malignant lesion of that size, probably will have spread by the lymphatics to such a degree as to preclude a surgical cure.

In a somewhat dogmatic way, I



prescribe

artamide

THE SAFE ANTI-ARTHRITIC AND ANTIRHEUMATIC THAT CONTAINS TH IMPORTANT PLUS OF ORGANIDIN® FOR THE FURTHER CONTROL OF I FLAMMATION AND TO AID IN THE RESORPTION OF NECROTIC TISSU

Sodium-free, potassium-free ARTAMIDE is especially valuable when clinical judgment precludes steroid therapy. ARTAMIDE provides higher salicylate blood levels[1] with lower dosage. Antirheumatic, anti-inflammatory, analgesic . . . ARTAMIDE aids normal corticosteroid activity. The inclusion of ORGANIDIN, the smoother, safer, organically bound iodine, greatly increases the effectiveness of the ARTAMIDE formula by stimulating the resorptive processes[2] and further controlling inflammation. **ARTAMIDE provides symptomatic relief as well as important gains in functional capacity for many patients who cannot tolerate corticosteroids.**

Each ARTAMIDE tablet contains: Salicylamide 0.25 Gm. (4 gr.); Para-aminobenzoic Acid 0.25 Gm. (4 gr.); Ascorbic Acid 20.0 mg. (⅓ gr.); ORGANIDIN® (iodinated glycerol) 20.0 mg. (⅓ gr.).

DOSAGE: 2 tablets 3 or 4 times daily. Requirements may vary according to the response of the patient. SUPPLIED: ARTAMIDE Tablets, bottles of 100 and 500. REFERENCES: 1. Chambers, James O.: Clinical Medicine, 61:3 (1954) pp. 203-205. 2. Salter, W. T.: A Textbook of Pharmacology, p. 603, W. B. Saunders Co. (1952).

WRITE: Professional Service Department for literature and trial supply.

WAMPOLE LABORATORIES, STAMFORD, CONNECTICUT

shall give my own interpretation of the factors on which I make a decision with reference to surgery:

1. The patient over age 50 years, whose gastric distress occurs for the first time is more likely to have cancer than one who has had such symptoms for many years, with previous x-ray demonstrations of ulcer-like lesions of the stomach or duodenum. Rhythmic epigastric distress with food- and alkali-relief suggests a benign lesion, but does not exclude cancer. Recent severe gastric hemorrhage is more suggestive of a benign ulcer.

2. The physical examination rarely aids in the recognition of early gastric cancer.

3. The x-ray examination is the most important single study in the differentiation.

The presence of a duodenal ulcer in a patient with a gastric ulcer favors the probability of a benign gastric lesion. The diagnosis finally must rest on the characteristics of the gastric lesion itself.

4. In the presence of achlorhydria, any gastric lesion, especially an ulcer, is to be regarded as malignant until proven otherwise. For this purpose, the conventional bread-and-water meal is used. If no hydrochloric acid is found, histamine stimulation is used and the test is repeated. If any free hydrochloric acid is present, the degree of acidity bears no relation to the nature of the lesion.

5. Gastroscopy often furnishes a clue to the diagnosis, the value varying with the experience of the observer.

6. An expert cytological study of the removed gastric contents has value in large polypoid gastric cancers, but this value is less in differentiating lesions resembling gastric ulcer. The brush techniques represent an advance but results are still disappointing. The report of grade-4 cancer in gastric contents is the equivalent of a biopsy.

A case with preponderance of evidence favoring a benign lesion will be put on a medical program for two weeks. All other cases go to surgery. The rate of healing may generally be taken as an index of benignancy. However, benign gastric ulcers have failed to heal over a period of five years. Such failure may occur in elderly persons, usually the size of the crater not varying on repeated x-ray examinations. Generally a benign gastric ulcer in a younger person will heal completely, two-thirds, or a half, during two weeks of a strict hospital program of bed rest, hourly milk feedings, hourly amphoteric antacid, and the judicious use of anticholinergic drugs and sedation. Very rarely a malignant ulcer seems to heal partially. In case satisfactory healing has not occurred in the two-week period, operation is recommended. If the ulcer apparently heals and shortly thereafter recurs, surgery should be resorted to.

Using the plan outlined, the number of instances of malignant ulcer overlooked should be extremely small, and the end results should compare favorably with a program of treating all gastric lesions surgically.

In summary, on basis of history, x-ray study, gastric analysis, gastroscopy and gastric cytologic study, if the findings are consistent with a benign ulcer, a strict medical program is adopted. If any of these studies suggest cancer, surgery is advised at once. If at the end of two weeks of the medical program, the ulcer heals par-

tially or completely, we are encouraged to continue a medical program with frequently repeated x-rays. If the ulcer fails to heal completely within a month, or recurs at any time in the same spot, surgery is urged.

On this plan, the patient is not being subjected to unnecessary surgery, and we have been largely successful in eradicating our early cancerous ulcers.◀

Bull. New York Acad. Med., 35:157-161,1959.

Warning on New Cancer Drug

The Cancer Chemotherapy National Service Center has reported that mitomycin C, an antibiotic reported as giving promising results in cancer treatment in Japan, has frequently produced major toxic reactions but seldom objective improvement in clinical trials in the United States. The antibiotic has been under clinical evaluation in this country as an antitumor agent in a substantial variety of tumors. In view of the effects observed in three current studies, it has not replaced the standard chemotherapeutic agents in any form of cancer. Studies are being continued and full reports on the clinical trials will appear later in the scientific literature.

Editorial Note, *New York J. Med.*, 59:1244,1959.

Comparative Effectiveness of Codeine Phosphate and Dextro-Propoxyphene Hydrochloride

Although analgesic effectiveness was almost the same, side effects were more frequent with codeine phosphate

WILLIAM L. WILSON, M.D., HARLEY DEERE, M.D., and VINCENT C. DESIDERO, M.D., *Philadelphia, Pennsylvania*

Analgesics are difficult to classify according to patient response since results are almost always subjective rather than objective. To reduce this difficulty in the present study, both the codeine phosphate and dextro-propoxyphene hydrochloride were employed in identical pink capsules of 32 and 64 mg. The medication was coded by a single individual so that the prescribing physicians and hospital personnel dispensing the medications were not aware of which was being taken.

METHOD OF STUDY

A total of 140 patients were selected. Of these 90 were post partum and 11 orthopedic cases (fractures and herniated intervertebral disks), 14 had pulmonary disease (pneumonia, infarction, and empyema), 14 metastatic malignant disease, and 11 miscellaneous disorders. Post partum patients were given 32 mg. of one of the drugs four times daily, starting immediately after delivery and continuing for two days. On the third day the other medication was started

and given until time of discharge, usually on the fifth day. The remaining 50 patients were maintained for a minimum of eight days, the same drug being given for three consecutive days. Of this group, 29 received the 32 mg. and 21 the 64 mg. preparations, either four times daily or every four hours. In all patients analgesic effectiveness was scored according to the degree of pain relief obtained over the preceding day, 50 points being given for very superior relief, 40 for superior, 30 for equivocal, 20 for inferior and 10 for no relief.

RESULTS

Pain relief obtained with both drugs showed a difference of only 10 points, indicating virtually identical analgesic effectiveness. Side effects occurring with both drugs included headache, nausea and vertigo in the post partum patients and constipation, vertigo, and drowsiness in the remaining patients. Urticaria developed in one post partum patient after having received codeine phosphate only. The most significant difference between the two drugs was the increased incidence of constipation noted when higher doses of codeine phosphate were employed.◀

Pennsylvania M.J., 2:186-187,1959.

Serum Cholesterol Reduction with Vegetable Oil-Pyridoxine Emulsions

Significant results cannot be expected without the reduction of saturated fats in the diet

RICHARD PERKINS, M.D., IRVING S. WRIGHT, M.D., and BARBARA W. GATJIE, B.S., *New York, New York*

Sustained reductions in serum lipid levels have been achieved when unsaturated vegetable oils were substituted for saturated animal fat in the human diet. Several vegetable oil emulsions have been employed in the treatment of hypercholesteremia and arteriosclerosis because of this activity, those of safflower and corn oil being most commonly employed at present. Several of these emulsions now available contain pyridoxine, which also may be involved in fat metabolism.

To test the serum cholesterol-reducing activity of safflower and corn oil emulsions with pyridoxine, 22 healthy male subjects ranging in age from 22 to 26 were given the preparations in addition to their regular diets. Half the volunteers were given the safflower and half the corn oil emulsion. The safflower oil emulsion contained 45 Gm. safflower oil and 50 mg. pyridoxine hydrochloride, and the corn oil emulsion 45 Gm. corn oil and 20 mg. pyridoxine hydrochloride per daily dose.

Questionnaires were used to establish total calorie intake, calories derived from fat, and total daily fat intake. The subjects adhered to their

regular diets throughout the study but were allowed to omit dessert if it caused them to gain weight. Serum was obtained weekly by venipuncture and analyzed for total serum cholesterol by a modified Bloor method. A five-week control period was established prior to therapy, at the end of which the subjects were matched according to the nearest average serum cholesterol levels observed during that time.

After seven weeks of therapy, the experimental groups were reversed, those having taken the safflower oil emulsion taking the corn oil emulsion and vice versa. Therapy was continued for 14 weeks, one week after which a final serum cholesterol determination was done on each subject.

RESULTS

During the five weeks without therapy, cholesterol levels ranged from 125 to 311 mg./100 cc., averaging 221 mg./cc. Addition of the safflower oil-pyridoxine emulsion in 11 subjects caused a slight decrease in the average serum cholesterol level, which continued when the corn oil-pyridoxine emulsion was substituted after seven weeks. Similar results were obtained with the 11 subjects in whom the sequence of therapy was reversed. Both groups showed slightly lower serum cholesterol levels when receiving the corn oil-pyridoxine emulsion.

COMMENT

The results obtained support the contention that a lowered serum cholesterol level is best achieved with safflower and corn oil emulsions when they are employed as supplements in diets markedly reduced in saturated fats.◀

J.A.M.A., 169:1731-1734,1959.

Recent Advances in Anesthesia

Great forward strides have been made in this highly specialized field, promoting greater surgical safety

HOWARD P. SAWYER, JR., M.D., *Portland, Maine*

REGIONAL ANESTHESIA

As a local anesthetic, procaine hydrochloride has withstood the test of time. Nevertheless the search continues for a more potent, less toxic, longer acting drug with a shorter duration and greater spreading properties. Some say that lidocaine comes close to fulfilling those requirements, but chlorprocaine may come even closer.

The subarachnoid injection of alcohol for the relief of the severe pain of terminal cancer has been expanded. The neurolytic action of alcohol provides a comparatively high incidence of pain relief which may be immediate or delayed for a few days and generally lasts for several weeks or months, after which the injection may be repeated.

A careful neurological examination is mandatory to properly identify the spinal cord segments involved, following which 0.5 to 1.0 cc. of 95 per cent alcohol is injected at each segment at a rate of 0.1 cc. per minute, preferably with a tuberculin syringe. Proper positioning of the patient, low specific gravity of the alcohol and its slow injection provide accurate localization of the neurolysis to the desired dorsal sensory roots. Reported complications include meningismus, adhesive pachymeningitis, rectal incontinence and paresis if the anterior motor roots are blocked.

PREMEDICATION AND GENERAL ANESTHESIA

The routine preoperative narcotics, particularly in the pain-free patient undergoing elective surgery, has lately been condemned by anesthesiologists because of the circulatory and respiratory depressing effects. The status of tranquilizers is unsettled.

The widespread use of corticosteroids has introduced a serious problem in patients coming to surgery who have taken one of the steroids, especially adrenal cortical hormone, at one time or another within the previous year.

Reports are few concerning the dangers of severe hypotension during anesthesia in patients whose hypertension is being treated with one of the rauwolfia derivatives, but experiences are coming to light indicating that sudden and profound drops in blood pressure with or without bradycardia are not uncommon. The bradycardia usually responds to atropine intravenously and the hypotension is reversed with an infusion of dilute norepinephrine which may have to be continued for several hours postoperatively. It might be well to delay elective surgery until the drug has been stopped for 10 to 15 days.

The ability of the "poor risk" patient to withstand major surgery while under very light anesthesia has been amply demonstrated with nitrous oxide and with ether. The analgesic first stage has been extended to include three planes wherein a patient undergoing major surgery is able to respond to commands, although completely free of pain and of any memory of the procedure.

MONITORING DEVICES

Blood pressure, pulse and respiration are recorded during surgical operation.

An operating room cardioscope shows the electrocardiographic pattern on an oscilloscope screen encased in an explosion-proof housing, and may be permanently recorded on an ordinary electrocardiograph located in the corridor.

Ventilation meters indicate tidal volume; infra-red analyzers measure exhaled carbon dioxide; thermistors indicate rectal or esophageal temperature; breath sounds are amplified, visual and/or auditory signals are activated by peripheral pulse or the heart's electrical output. A still reliable, simple and useful device is a stethoscope fixed over the precordium using a comfortable, single molded plastic earpiece.

ANESTHETIC AGENTS

Trichlorethylene, introduced in 1941, is becoming more widely used. It is potent and volatile, yet not irritating, while producing amnesia and a high degree of analgesia in light anesthesia.

Fluothane is four times as potent as diethyl ether; its safe administration requires special finely-adjustable vaporizers since very small changes in its concentration will produce profound changes in the depth of anesthesia. It is not for use by the untrained or part-time anesthetist.

ANTAGONISTS

Narcotic antagonists have proved their value, but are contraindicated in depression due to anything except a narcotic. In obstetrics they have been given prior to delivery to overly narcotized mothers or to depressed infants via the umbilical vein. The respiratory depression of narco-

tics used in anesthesia to supplement nitrous oxide may be minimized without affecting analgesia, by adding an antagonist in the proper ratio for whatever narcotic is used.

HYPNOSIS

More than 300 operations are reported to have been done under hypnosis alone. Ten per cent of all individuals are completely unaffected by hypnosis; 25 per cent can be put into a light trance without analgesia; 35 per cent can be put into a medium trance suitable for minor surgery and 20 per cent can be put into a deep trance adequate for major surgery.

CONTROLLED HYPOTENSION

In order to reduce blood loss during surgery and also to provide an almost bloodless field, blood pressure has been deliberately lowered by various methods. Pharmacological blockade with one of the methonium compounds or a thiophanium derivative is probably the method of choice as its brief action makes it fairly controllable when administered in a 0.1% solution in normal saline or with 5% dextrose in water. Controlled hypotension is not without its dangers and should be reserved for those cases which would be extremely difficult without it and where no contraindications exist, such as chronic hypertension with renal or pulmonary disease, angina or coronary insufficiency, shock or Addison's disease.

HYPOTHERMIA

The pervascular method of cooling removes blood from the arterial circulation, cools it in a coil and returns it to the venous side.

Body cavities may be perfused with cold solutions. If the need for hypothermia arises after the pleural cavity has been opened it may be perfused with cold saline. In England early attempts to perfuse the stomach resulted in considerable loss of electrolytes until a plastic bag combined with a tube allowed heat transfer but kept the cold solution from direct contact with the gastric mucosa. Most widely employed are forms of body surface cooling, using blankets with circulating coils, or immersion in ice water after the patient has been anesthetized. Similar methods may be employed for rewarming when surgery has been completed.

SUMMARY

Emphasizing the close relationship and interdependence of surgery and anesthesiology, some of the more important advances of the past few years in anesthesia have been briefly described. These include new drugs for local and for general anesthesia, methods of monitoring a patient during operation, the use of muscle relaxants and lighter levels of anesthesia, narcotic and barbiturate antagonists, hypnosis, controlled hypotension and hypothermia.◀

J. Maine M.A., 49:293-296,1958.

NEW

1 mg. Tablets

STELAZINE*

brand of trifluoperazine

For b.i.d. administration

FOR ANXIETY—
PARTICULARLY WHEN EXPRESSED AS APATHY, LISTLESSNESS AND EMOTIONAL FATIGUE

often effective where other agents fail

*

enthusiastic patient acceptance

*

fast therapeutic response with very low oral doses

*

convenient b.i.d. administration

*

side effects usually slight and transitory

*Trademark

Clinically evaluated, before introduction, in over 12,000 patie

SMITH
KLINE &

Treatment of Systemic Scleroderma

Some suggestions are presented for the treatment of the patient who manifests systemic scleroderma

R. K. WINKELMANN, M.D., *Rochester, Minnesota*

The patient with systemic scleroderma, knowing the gravity of the disease, is eager to receive any form of active therapy, and the physician is usually enthusiastic and uncritical in trying a new drug. Since the disease process varies from day to day, it is difficult to measure changes in the basic signs of the disease in a short period.

The purpose of treatment is to control vasomotor changes and to resolve edema and sclerosis so far as possible. If the environmental temperature is kept at 76° F., vasomotor episodes may cease spontaneously. The housewife must not put her unprotected hands into the freezer or hang out wet clothes on a windy day. Dibenzyline, 10 mg. three to six times daily, may suppress the episodes and warm the fingers. Alcoholic drinks are welcomed and warming. If Raynaud's reaction exists, or emotional excitement causes attacks, a tranquilizer may be helpful. Local heat and massage in graded series helps to maintain function.

Twenty-three patients were treated with relaxin, with resolution of edema and sclerosis, healing of trophic ulcers, and some control of the Raynaud crises. They observed no effect on visceral lesions. Relapse is usual on discontinuance. The hormone is scarce and high-priced.

A course of disodium versenate, 50 gm. in daily dose of 50 mg. per kg. of

body weight, by slow intravenous drip, benefits many patients. Blood calcium is estimated at the beginning of therapy. No symptoms of tetany have been observed during slow administration of the drug. Estimation of urinary calcium has showed that the drug is 80 to 90% efficient in removing calcium from the tissues. No coagulation defects have been found during therapy. Renal irritation may occur, but will usually subside with an extra day of rest.

Treatment of scleroderma with chelating agents has been considered useful in patients with acrosclerosis. Four of nine such patients were considerably improved. Esophageal motility reverted almost to normal in one at the end of three months. Four patients' ability to sit, stand, walk, and move portions of the body improved significantly. All nine had less edema during treatment. A patient with diffuse scleroderma and one with generalized morphea did not respond to therapy. Chelating agents are effective primarily in acrosclerosis of slow progression, a group in which therapeutic effects are difficult to evaluate.

Severe limitation of function of the involved parts makes it imperative that the discomfort be kept at a minimum. Use of antacids and elevation of the head of the bed benefit those with esophageal involvement. Pancreatin aids some patients who have intestinal symptoms. Appropriate measures for cardiac, renal and respiratory symptoms are occasionally necessary. Co-existing diseases should be treated exactly as if the patient did not have scleroderma. Surgical procedures may be performed if cardiac and renal function are adequate.

Steroids reduce arthralgia and edema, increase the sense of well-being and occasionally aid appetite, but have no effect on the sclerosis. Some patients with acrosclerosis have been given steroids for as long as five years without any effect on the sclerotic process. Such treatment only produces steroid invalidism. Serious deliberation should precede the use of steroids for scleroderma. Small doses may be helpful to increase appetite, improve respiratory function or increase the sense of well-being, but such therapy should not be used with the idea of changing the basic disease process.◀

Proc. Staff Meet., Mayo Clin., 34:55-58,1959.

Syphilitic Fetus After Prenatal Penicillin Therapy

A woman of 32 attending an antenatal clinic showed serological syphilis test positive at the 16th week of pregnancy. Fetal movements ceased 5 weeks later. Crystalline sodium penicillin, 1,000,000 units daily, was given for 15 days beginning with the 22nd week. Miscarriage of a macerated fetus occurred in the 27th week, and postmortem examination of the fetal liver showed the presence of many spirochetes with the morphology of Treponema pallidum. Examination of the husband revealed latent syphilis. Antisyphilitic treatment should be given immediately to expectant mothers in whom the initial serologic test for syphilis is positive.

Burgess, J. A., *Brit. J. Ven. Dis.*, 34:240,1958.

Nonsurgical Treatment of Fecal Incontinence

Diet, drugs, irrigation of the intestine, anal muscle exercises and psychotherapy are recommended

RAYMOND J. JACKMAN, M.D., *Rochester, Minnesota*

The diet should be easy to follow of a low-residue type. The patient should have a list of foods to be included in the diet and a list to be excluded. Limit liquid, give minimum-residue diet with vitamin supplementation.

The patient should have drugs that decrease intestinal peristalsis and those that "soak up" water from the intestines, thus giving more form to the stool. Tablets containing ¾ grain of phenobarbital with 1/250 grain of the alkaloids of belladonna, have been satisfactory. Usually, half of such a tablet before each meal is an adequate dose. This is particularly indicated in patients who have the irritable-colon syndrome or when emotional upsets precipitate a bout of diarrhea. Other anticholinergic drugs of value are methantheline bromide, 50 mg. after each meal, or propantheline bromide, 15 mg. after each meal.

Methycellulose, given as 0.5 gm. tablets, has a power of "soaking up" water and giving the stool form. The doses must be individualized; 3 to 6 tablets after each meal with a limited intake of fluids is usually of value. Many patients respond well to drug therapy.

Irrigation of the lower part of the intestine when there is seepage or leakage through out the day is a problem. After the initial stool of the day, the patient "washes out" the lower intestine with warm water. In-

REDUCE BLOOD LOSS DURING SURGERY

KUTAPRESSIN®

Kutapressin, a fractional derivative of liver, minimizes capillary oozing and often reduces the need for transfusion.

Surgical procedures, such as tonsillectomies and adenoidectomies, transurethral resections, and even ophthalmologic and brain surgery, are facilitated by improving visibility within the surgical field. The incidence of postoperative hemorrhage is likewise significantly reduced.

In all surgical procedures, Kutapressin promotes better wound healing. Kutapressin does not affect systemic blood pressure, blood clotting or prothrombin time, and there are no untoward effects following its use.

Kutapressin is administered intramuscularly or subcutaneously. Available in 10 cc. and 20 cc. multiple dose vials.

send for reprints and literature

Prescribe with Confidence

KREMERS-URBAN COMPANY • *Milwaukee 1, Wisconsin*

Ethical Pharmaceuticals Since 1894

stead of an enema tip, an 18 F. to 26 F. catheter is used because it can be inserted higher into the rectum and trauma is less likely. Practice in holding the water improves performance. A large anal defect requires a Bardex-Foley type of rectal bag and catheter. The patient should be instructed to press the distended Bardex bag against the perineum to close the anal defect.

For several years roentgenologists make the incontinent patient retain barium during studies on the colon. To do this, a hole is drilled through the center of a soft-rubber ball (size of a tennis ball) and the catheter is pushed through the hole in the ball which is pressed against the defect so that water is retained. This simple equipment has been extremely valuable for many patients with anal deformities and defects who have difficulty retaining enemas. If much stool is expelled with the first irrigation or enema, the patient repeats it a second or even a third time. Since many of these patients are elderly, their first attempt at the procedure should be under the supervision of a nurse or physician.

The irrigation rids the lower intestine of stool, so that the patient is less likely to have leakage. Most of these patients have scar tissue in the anorectal region that makes the muscle less efficient. The warm irrigating fluid aids in making this scar tissue more resilient, and the mere practice of trying to retain the warm water will help to strengthen the muscles in that region.

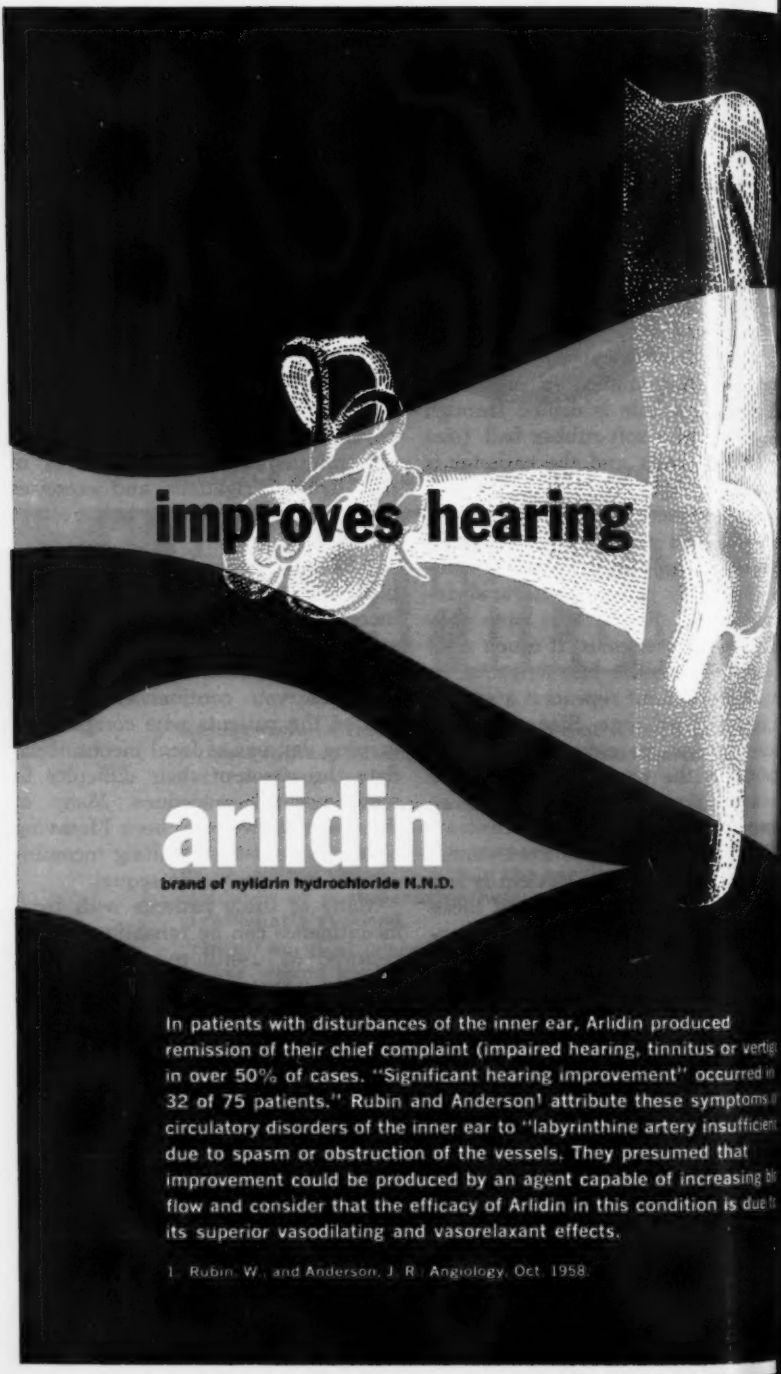
The patient should be instructed to exercise the regional muscles three times daily for five minutes while lying down. The external sphincter is contracted and held in this state while the patient counts slowly to five; then repeated. Have the patient demonstrate this contraction while on the table. These exercises should be continued for two or three months.

Of two persons with the same degree of anal incontinence, one may ostracize himself, the other be little, if any, concerned. Similar variations in reaction occur in women who have rectovaginal fistulas. Many of these patients have acquired the habit of wearing a diaper, which is unsound psychologically. This habit is to be discontinued after the measures of diet, drugs, irrigations, and exercises are started, in order to help restore confidence.

Although surgical treatment has a place in helping the patient with fecal incontinence, its results frequently are not satisfactory. This is particularly true in patients who have no or poor reservoir continence. At least half of the patients who complain of varying degrees of fecal incontinence date the onset of their difficulty to some surgical procedure. Many of these operations have been lifesaving measures, and the resulting incontinence is an unfortunate sequel.

Many of these patients with fecal incontinence can be rehabilitated and restored as useful members of society by a systematic plan of nonsurgical treatment, consisting of diet, drugs, irrigation of the lower part of the intestine, exercises for the anal muscles, and psychotherapy. These measures are used singly or in combination, as each patient's particular problem dictates.◀

J.A.M.A., 166:1281-1285,1958.


improves hearing
arlidin
brand of nylidrin hydrochloride N.N.D.
In patients with disturbances of the inner ear, Arlidin produced remission of their chief complaint (impaired hearing, tinnitus or vertig in over 50% of cases. "Significant hearing improvement" occurred in 32 of 75 patients." Rubin and Anderson[1] attribute these symptoms o circulatory disorders of the inner ear to "labyrinthine artery insufficien due to spasm or obstruction of the vessels. They presumed that improvement could be produced by an agent capable of increasing bl flow and consider that the efficacy of Arlidin in this condition is due t its superior vasodilating and vasorelaxant effects.
1. Rubin, W., and Anderson, J. R.: Angiology, Oct. 1958.

Is Hydrotherapy of Value?

The author refutes the usefulness of hydrotherapy per se, and suggests further controlled clinical trials

R. HARRIS, M.D., *Buxton, England*

A massive volume of experimental work has been performed on the physiological effects of various applications of water as baths, douches and sprays—hot, cold, neutral or alternating. The results have been evaluated by ergometry, plethysmography, electrocardiography and biochemistry, and by study of the blood pressure, pulse or respiration rate, urine volume and analysis, blood sugar and leukocyte count.

NO ACCURATE ASSESSMENT

Accurate assessment has not been made of the clinical value of these proceedings. This is not surprising. Hydrotherapeutic measures have, in general, been used in conditions with obscure pathology—chronic rheumatism, sciatica, fibrositis—conditions well known to have variable courses, but usually self-limiting. In these, the enthusiasm of the physician and the impressive ritual of hydrotherapy are valuable additions to the therapeutic effects of water. In the great days of spas, hydrotherapy was considered to be a complete system of medicine and used for every illness. Often no treatment other than water internally and externally was given. Unfortunately neither the diagnostic criteria of that era nor the methods of assessing clinical results are acceptable to us.

Today hydrotherapy is used in conjunction with other forms of physical treatment, with drugs and general

care. The tendency is still to use it in conditions of inexact diagnosis and pathology, and of relatively unknown natural history and prognosis. These are conditions in which quackery thrives, and in which accurate assessment of progress is so notoriously difficult. In these diseases even the clinical effect of drugs is difficult to evaluate.

Recently an attempt was made to assess the value of wax baths in the treatment of the hands of in-patients with rheumatoid arthritis. Despite a complicated and detailed compartive study of 100 subjects followed for six weeks, the results showed little difference between the treated and untreated groups.

The internal use of water, by either drinking prescribed amounts of spa water or introducing it into the body cavities, has largely been abandoned. The two principal aspects of current use of water are as an exercise medium, and as a means of applying thermal or mechanical stimulation.

THE THERAPEUTIC POOL INDISPENSABLE IN CERTAIN CASES

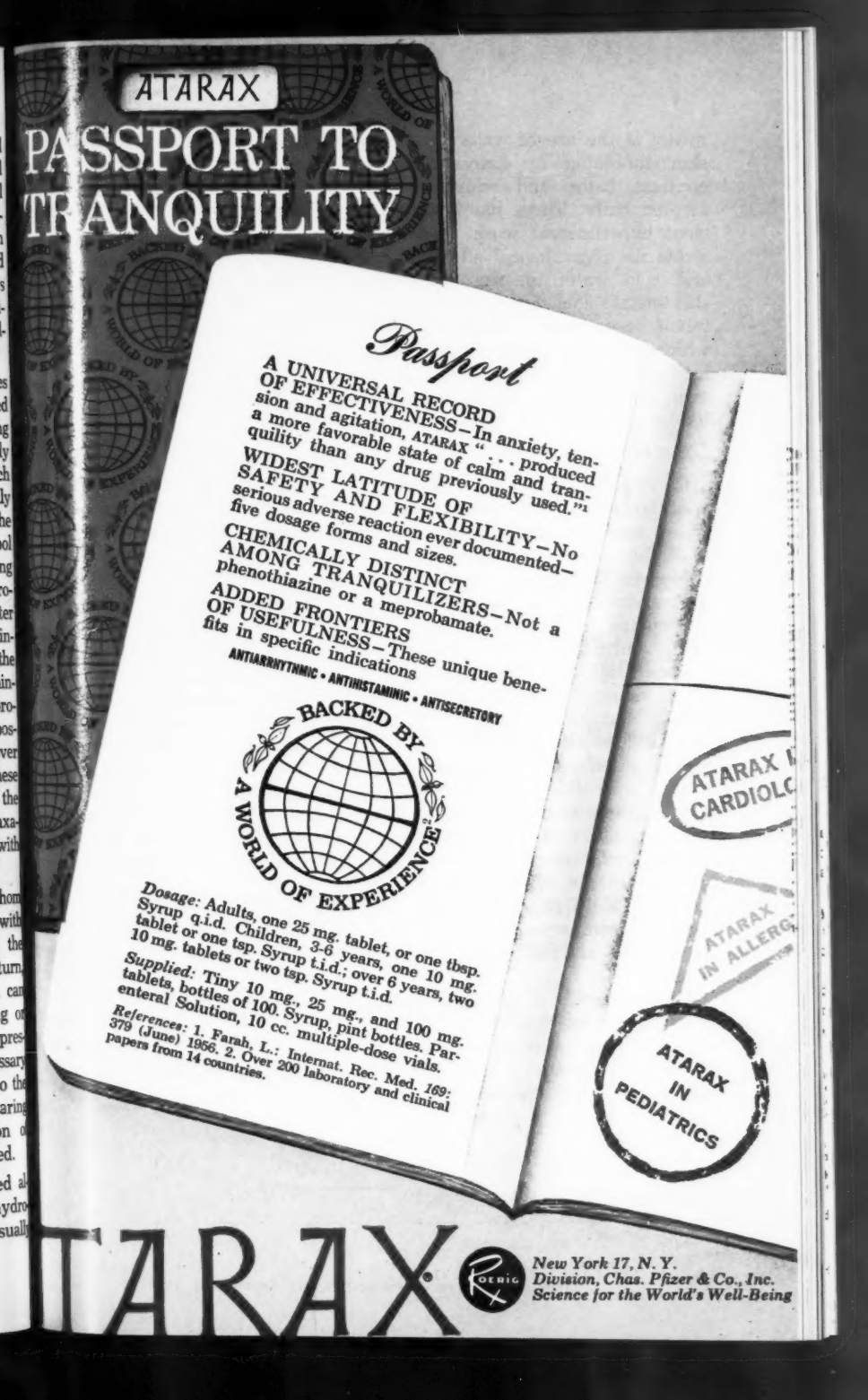
In every condition where the force of gravity is too great a handicap for weakened muscles, the therapeutic pool is indispensable. Any hospital handling locomotor disabilities, whether rheumatic, traumatic or neurogenic, and units where reconstructive and orthopedic surgery is practiced, needs pool facilities for exercise.

Will a patient with poliomyelitis gain his maximal muscle power and function more quickly by exercise in water than by "dry" resisted exercise? Will the end point be the same? The patients themselves feel that exercise in water is more beneficial to them, and they would rather miss any other form of treatment than pool therapy. Patients with rheumatoid arthritis can start walking in the pool when they are not capable of weight-bearing, or even standing alone, on dry land. Clinical impressions and common sense indicate that this is valuable and probably leads to earlier "real" walking—but is this actually so?

Relaxation of spastic muscle takes place in warm water. Is it maintained for any useful period after leaving the pool, or can it be more efficiently produced by simpler techniques such as dry heat, or moist packs? Recently an attempt was made to measure the relaxation produced by warm pool therapy in patients with ankylosing spondylitis. The patient's spinal profile was plotted with a posture-meter before and immediately after 30 minutes' relaxation and exercise in the deep pool, and after a further 30 minutes of hot packing. The serial profiles showed real improvement in posture at each stage, and a gain of over one inch in height. However, these measurements were repeated on the same subjects before and after relaxation exercises in the gymnasium with almost exactly similar results.

Another group of patients for whom the pool has been used are those with peripheral vascular diseases. In the limb with inadequate venous return, where stagnation and ulceration can only be controlled by bandaging or elastic stockings, the external pressure of water supplies the necessary support. Exercise can be given to the foot and ankle in the weight-bearing position without the restriction of bandages, and the ankle mobilized.

The use of pools has received almost universal favor. When hydrotherapy is criticized, what is usually


ATARAX
PASSPORT TO TRANQUILITY
Passport
A UNIVERSAL RECORD OF EFFECTIVENESS—In anxiety, tension and agitation, ATARAX "... produced a more favorable state of calm and tranquility than any drug previously used."1
WIDEST LATITUDE OF SAFETY AND FLEXIBILITY—No serious adverse reaction ever documented—five dosage forms and sizes.
CHEMICALLY DISTINCT AMONG TRANQUILIZERS—Not a phenothiazine or a meprobamate.
ADDED FRONTIERS OF USEFULNESS—These unique benefits in specific indications
ANTIARRHYTHMIC • ANTIHISTAMINIC • ANTISECRETORY
BACKED BY A WORLD OF EXPERIENCE
Dosage: Adults, one 25 mg. tablet, or one tbsp. Syrup q.i.d. Children, 3-6 years, one 10 mg. tablet or one tsp. Syrup t.i.d.; over 6 years, two 10 mg. tablets or two tsp. Syrup t.i.d.
Supplied: Tiny 10 mg., 25 mg., and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.
References: 1. Farah, L.: Internat. Rec. Med. 169: 379 (June) 1956. 2. Over 200 laboratory and clinical papers from 14 countries.
ATARAX
ATARAX IN CARDIOLO
ATARAX IN ALLERG
ATARAX IN PEDIATRICS
ATARAX
Roerig Rx
New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

meant is the use of water to supply skin stimulation by sprays, douches, contrast baths and whirlpool and aerated baths. There has been sufficient experimental work to demonstrate the physiological effects of hot and cold water on the body. The short-acting cold douche produces an initial peripheral vaso-constriction which is followed by hyperemia and a feeling of well-being. There is, however, no clinical evidence to support its use in prophylaxis or in therapy.

CONTRAST BATHS

Contrast baths, in which limbs are alternately immersed in hot and cold water, have traditionally been used in conditions in which vascular spasm is present. There is no evidence that the passive exercise of dilating and constricting skin vessels has any value, and indeed it is probable that the benefit, if any, is due to the warm phase alone and that the cold phase may be dangerous.

In 1952 the effects of contrast baths on the vasomotor response of rheumatoid arthritics was studied. Although after a course of treatment the cold sensitivity of the rheumatoids was reduced, there was little evidence of re-education of the skin vessels, there was no correlation between this and clinical improvement and none of the patients showed marked clinical relief.

A critical study of blood flow measurements comparing effects of hot whirlpool and nonagitated baths at the same temperature has shown no difference between the two. However, it is again common experience tha these baths feel more comforting t the patient and can be tolerated a higher temperatures.

Is the mechanical stimulation o falling water, of air bubbles, of rapid ly altering thermal stimuli of value Counter-irritation is a great standby of physical therapy, but again care fully controlled evaluation is lacking

MENTAL HOSPITALS NO LONGER HAVE HYDROTHERAPY DEPARTMENTS

In the era before phenobarbiton and the tranquilizers, the mental hos pitals found the neutral bath a valu able sedative. The hydrotherapy de partment, like the padded cell and th strait jacket, has disappeared from th mental hospitals.

What are we left with in hydrother apy? There is nothing in use of whic the clinical value has been demon strated by trials which will stand u to critical assessment. We have onl overall clinical impressions—that ex ercise and relaxation in warm wate is useful in the locomotor disease and disabilities, and that the mor exotic forms of hydrotherapy com bined with spa ritual are useful i psychosomatic disorders.

CONTROLLED TRIALS IN ORDER

Controlled clinical trials are u gently required in hydrotherap These must be done on a multi-cente basis so that adequate numbers cases can be studied in a reasonab time and single and relatively simp problems dealt with one at a time.

Proc. Roy. Soc. Med., 51:94-96,1958.

highlights of a nationwide survey

A REPORT
ON THE TREATMENT IN PRIVATE PRACTICE
OF 2,274 PATIENTS
WITH ALLERGIC DISORDERS

RESULTS OF ANERGEX THERAPY BY 202 PHYSICIANS IN PRIVATE PRACTICE

disease classification	no. of patients treated	excellent	good	fair	not improved
allergic rhinitis:					
perennial	492	196	176	67	53
spring	209	80	85	31	13
fall	248	87	114	35	12
spring & fall	198	73	77	19	29
		77%			
extrinsic asthma	492	175	178	68	71
		72%			
eczema	260	119	71	42	28
		73%			
food allergy	173	85	42	13	33
		73%			
contact dermatitis	157	54	62	23	18
		73%			
other	45	17	15	1	12
		71%			
total patients treated	**2274**	**886**	**820**	**299**	**269**
		75%			

These results were obtained following a single short course of injections.

Compiled from questionnaires sent to practicing physicians in communities of various sizes throughout the country, who were asked to indicate the number of patients they had treated, and to classify the results as Excellent, Good, Fair or Unimproved.

Many physicians not only supplied the bare statistics but added comments such as:

"In cases with good results—they were spectacular—in others not too definite." (California)

"Not impressed." (5 patients) (Louisiana)

"I find it to be a wonderful drug." (Indiana)

"Has been a very useful medication especially in infants where multiple testing is impossible." (Ohio)

"We seem to notice greater degree of success in younger patients. No response to treatment in dermatitis cases." (Illinois)

"Three cases of eczema under the age of 3 years, all were controlled on Anergex." (Wisconsin)

"I have thus far had nothing but excellent results except one failure in contact dermatitis." (Ohio)

"Both patients who displayed good results in rhinitis had been given desensitizing injections preseasonally." (Pennsylvania)

"All of these patients had previously shown poor results on cortisone, antihistamines and desensitization." (Illinois)

"We have used it for two years. One of the excellent results (asthma) was on myself." (Pennsylvania)

"No benefit." (2 patients) (Michigan)

"Results impressive." (Iowa)

"Good results in Hay Fever—from children to elderly group." (Iowa)

"We are really happy with this product." (Washington)

Chlorothiazide in Hypertension

The principal value of this drug appears to be enhancement of the antihypertensive effects of other agents

EDWARD D. FREIS, M.D., *Washington, D. C.*

It was recently discovered that chlorothiazide had a potent salt-depleting or saluretic effect in animals, an observation confirmed in edematous patients. The loss of both sodium and chloride in the urine after a dose of 1 to 1.5 gm. per day orally is ordinarily as great as after an optimal parenteral dose of a mercurial. Side effects are only those directly attributable to diuretic action.

In 10 hospitalized hypertensive patients given 500 mg. three times daily for six days, reduction of mean pressure averaged 16 per cent. In 73 patients in whom chlorothiazide, 500 mg. twice daily, was added to regimens which included rauwolfia, rauwolfia-hydralazine, veratrum viride, or the ganglionic blocking agents, reduction of mean pressure averaged 27 per cent. Average pretreatment blood pressure for the 73 patients was 211/126; after therapy with chlorothiazide plus other agents it was 153/98, although ganglionic blocking drugs were discontinued in 19 of 32 patients (but with continuation of reserpine and/or hydralazine), and reduced to one-half the previous dose in the remainder.

ADVANTAGES

The advantages of chlorothiazide are simple dosage schedule and scarcity of side effects. The drug can produce serious toxic effects in the average case of hypertension uncompli-

cated by renal or cardiac failure, but no significant toxicity was noted with a standard dose of 500 mg. on arising and 500 mg. at bedtime. No potassium supplements were used in these uncomplicated cases and, except for occasional transient nausea or weakness early in the course of treatment, no difficulties were experienced.

CONGESTIVE HEART FAILURE

Patients with congestive heart failure, however, not infrequently exhibit toxic manifestations. They lose more potassium in the urine than do normal persons, an effect enhanced by chlorothiazide. If the drug is given continuously, as it must be to maintain antihypertensive effect, significant hypopotassemia can result. Frequently extra systoles, bigeminy, A-V block, and various arrhythmias result from the combined effect of hypopotassemia and digitalis.

In treatment of hypertensive patients with congestive heart failure, if diastolic pressure is below 105, digitalis is continued and chlorothiazide, 1 gm., is given twice weekly, principally for diuretic effect. If diastolic pressure is above 105, chlorothiazide is given daily in the usual dosage along with rauwolfia, and, if necessary, a ganglionic blocking agent. If pressure is well controlled, digitalis usually can be discontinued without return of congestive signs and symptoms. Occasionally, a patient requires both antihypertensive drugs and digitalis, in which case dosage of the latter should be carefully adjusted and potassium supplements may be needed. Patients whose hypertension results from steroid therapy should not receive chlorothiazide since severe hypopotassemia can result.

RENAL IMPAIRMENT

When patients with serious renal impairment are given chlorothiazide, the blood urea nitrogen should be measured frequently and dosage reduced or withdrawn on significant elevation in these levels.

In patients who have undergone sympathectomy or in those being given ganglionic blocking drugs, blood pressure reduction may be profound. If, in addition, the patient has atherosclerosis of the cerebral or coronary blood vessels, the resultant severe hypotension could cause a cerebral or coronary thrombosis. Even in uncomplicated cases, ganglionic blocking agents should be cut in half when chlorothiazide is administered, then readjusted as necessary. In atherosclerotic patients, even greater caution is indicated. Frequent home recordings of blood pressure in patients who are receiving ganglionic blocking agents should be done.

USE IN UNCOMPLICATED HYPERTENSION

In uncomplicated hypertension, the type usually seen in office practice, chlorothiazide alone, 500 mg. twice daily, may be given for a week. If pressure reduction is inadequate, rauwolfia may be added. If response is inadequate, hydralazine may be added, 25 mg. three times daily, and increased gradually, if necessary, to but not beyond 50 mg. per dose. Chlorothiazide and hydralazine not to exceed 150 mg. per day is often effective, well tolerated, and free of serious toxic effects. This probably is the treatment of choice for mild and moderate hypertension, since the danger of emotional depression from long administration of rauwolfia alkaloids is avoided.

USE WITH BLOCKING DRUG

If a blocking drug is required, dosage can be regulated most effectively

n your patients tell you:
n't sleep," your
lable, conservative answer is

NOCTEC

NOCTEC

Squibb Chloral Hydrate

ERAL PRACTICE "The general practitioner likes it... can be given to patients of all ages and
al status"

DIOLOGY "patients with cardiac disease... no proof that it is deleterious to the heart"

HATOLOGY "frequently the favorite of the dermatologist... skin reactions from it are uncommon"

CHIATRY "The psychiatrist often finds it the agent of choice... much less likely to produce mental
ment"

Current Concepts in Therapy: Sedative-Hypnotic Drugs II. Chloral Hydrate. New England J. Med. 255: 706 (Oct. 11) 1956.

: 1 or 2 7½ gr. capsules or 1 or 2 teaspoonfuls of Noctec Solution 15 to 30 minutes before bedtime.
rs: 1 or 2 15¾ gr. capsules or ½ to 1 teaspoonful of Noctec Solution 15 to 30 minutes before bedtime.
: 7½ and 15¾ gr. capsules, bottles of 100. Solution, 7½ gr. per 5 cc. teaspoonful, bottles of 1 pint.

SQUIBB *Squibb Quality—the Priceless Ingredient*

in the hospital or, at least, with frequent recording of blood pressure in the home by the patient or a member of his family. Initial dosages should be low and increased gradually. Response of blood pressure in the erect position should be used as a guide to further dosage. Because of the increased responsiveness induced by chlorothiazide, dosages often can be kept small enough to avoid disturbing side effects. However, the usual precautions in regard to the use of ganglionic blocking agents, including use of laxatives to prevent constipation, are still required.

Most patients are more responsive to combinations of agents than to individual drugs. Among patients there may be variations from almost no response to extreme reduction of blood pressure.

The introduction of chlorothiazide represents another step toward the objective of ultimate control of hypertension. The drug's principal value seems to be enhancement of the antihypertensive effects of other agents.◀

Heart Bull., 7:105-107,1958.

Tendon Repair of the Hand

A divided tendon presenting in a wound seems to demand repair, and still, long experience has shown that this is frequently followed by failure. Secondary repair is always possible. All one can lose by postponing primary repair is three to five weeks of time. Considering what may be lost by unwise surgery, the price is not high. Unless the surgeon is entirely satisfied with the conditions, he should postpone tendon suture.

The initial treatment is the most important consideration, since the whole subsequent course depends upon the correct interpretation of the indications, and upon their meticulous completion. It takes courage to refrain from extensive nerve and tendon suture and to concentrate upon simple cleansing, excising, and closing the wound. It is difficult to explain this to a patient, because, to him, a hand injury is a simple affair and the repair but a minor procedure. It is sometimes difficult to make colleagues understand that unless conditions are just right, it is best simply to close a wound and postpone nerve and tendon repair.

Some types of injury, such as human bites, introduce dangerous invasive organisms and primary repair would be out of the question. One would hesitate to carry out tendon repair in a wound which had been tampered with. If over four hours time has elapsed since the injury, one should consider quite carefully whether or not primary repair is justified. The lacerated or the crushing wound, or wounds with fractures, are seldom, if ever, suitable for primary suture of tendons. Unless it is possible, following tendon repair, to cover the area with adequate skin flaps, primary repair is not permissible. The surgeon must have available the proper facilities in the way of assistants, instruments and suture material, and have the experience and training to carry out tendon repair and to supervise the after care. If the conditions are not correct for primary repair, there should be no hesitancy in deciding against it. No criticism can be attached to postponing tendon repair, under unfavorable conditions.

Mason, M. L., *Nebraska M.J.*, 44:151-153,1959.

Cause of Polio in Triply Vaccinated Individuals

Studies in over 4,000 children indicate that immunologic failure is due to varying vaccine potencies

JONAS E. SALK, M.D., *Pittsburgh, Pennsylvania*

In five seasons of observing the pattern of poliomyelitis in vaccinated and unvaccinated individuals, the question arises as to why some having received three doses of the vaccine still contract the disease. Possible explanations include:

1. Certain batches of vaccine may be of less than optimal potency.
2. Some persons may be unusually unresponsive, even though the vaccine is of optimal potency.
3. The immunologic response may have dissipated rapidly.
4. The poliomyelitis virus may have reached the central nervous system by a route other than the bloodstream, thereby bypassing the influence of the serum antibody.
5. The causative viral agent may be different from that specifically protected against by the vaccine.

FINDINGS IN CHILDREN

In 4,617 children having received three injections of commercially or laboratory prepared vaccine it was shown that, generally, that the larger the dose the greater the virus-neutralizing capacity found in the serum. It was also observed that antibody titers were considerably higher in the children receiving the laboratory prepared vaccine than in those receiving comparable doses of the commercially prepared vaccines. Antibody levels in these children remained constant one to two years following third

"...iodides
and hot liquids
–[among]
the best
friends
an asthmatic
ever had."[1]

FREE YOUR ASTHMATIC PATIENT FROM SECRETORY OBSTRUCTION

ENCOURAGE BRONCHIAL EVACUATION

ORGANIDIN®

solution and tablets — iodinated glycerol, organically bound iodine

THE WELL TOLERATED[1] IODIDE EXPECTORANT—"Wheezing" or "hacking" coughs respond most favorably to specific antitussive medication plus the "excellent bronchial evacuants" —iodides—a most clinically effective type of expectorant.[3] For excellent results, add stable Organidin—organically bound iodine—to your favorite cough therapy. Organidin is better tasting, better tolerated than inorganic iodides. Full dosage may be given immediately. ORGANIDIN solution is freely miscible with common syrups. **SUPPLIED:** Solution, bottles of 30 cc.; Tablets bottles of 100. **DOSAGE:** See Physicians' Desk Reference, 1959, p. 847. (1) Seltzer, A.: M Ann. District of Columbia **26**:17 (Jan.) 1957. (2) Segal, M. S.: J.A.M.A. **169**:1063 (Mar. 1959. (3) McLean, J. A.: GP **18**:128 (Dec.) 1958. For professional samples and literature write

inoculation. Similar variations were observed in 2,709 children having received three injections of three differently prepared vaccines.

ANTIBODY RESPONSE TO A FOURTH DOSE

For the group of 4,167 children, 462 showing little or no detectable antibody formation were given a fourth dose of laboratory-prepared vaccine. Additional paired serum samples were available from 63 children given a fourth dose of a commercially prepared vaccine by their own physicians.

Results in the 462 children showed a marked increase in antibody concentrations, in most instances comparable to the levels induced by a third dose when prior inoculations were made with vaccines of good potency. The group of 63 children given the fourth dose with a commercially prepared vaccine also showed marked increases in antibody levels.

PARALYTIC ILLNESS IN TRIPLY VACCINATED PERSONS

Stool specimens in 103 triply vaccinated patients collected within 14 days of onset of illness showed: Polioviruses in 55 (type 3 in 39, type 1 in 15, and types 1 and 3 in 1); Coxsackie A9 in 3, B3 in 1, B4 in 2, and B5 in 7; and ECHO-9 in 7. The remaining 28 specimens as yet have failed to reveal viruses, and are still being studied. Of the illnesses suggesting paralytic poliomyelitis and from which virus was isolated, approximately one-fourth were due to Coxsackie or ECHO organisms.

CONTROL OF VACCINE POTENCY

The foregoing observations point to vaccine potency as the critical variant in immunologic effectiveness. The role of unusually unresponsive persons cannot be evaluated fully until optimally effective vaccines are more readily available. From the present data, however, it appears that such individuals are rare.

Solution of the problem appears to be not one of multiple inoculations with weak vaccines, but rather the use of the smallest number of doses of an optimally effective vaccine. Potency testing procedures are currently undergoing revision to make vaccines of this type generally available.◀

J.A.M.A., 169:1829-1838,1959.

Gastro-Intestinal Trichobezoar

Trichobezoars of the gastro-intestinal tract are of sufficient rarity to warrant reporting of all cases. A case of trichobezoar of the stomach, duodenum and jejunum, with intestinal obstruction secondary to jejunal intussusception is reported in a negro of 27 with a history of ingestion of copious amounts of nylon cloth, rags, bristles, doll's hair, and wool rugs since she was able to crawl. The diagnosis is usually easily made from the history of the ingestion of foreign material and hair, and characteristic radiographic findings. Treatment is primarily surgical removal and psychiatric later care. An additional case of trichobezoar of the gastro-intestinal tract is added, making a total of 231 cases in the literature. This case also presents the unusual complication of intussusception of the jejunum, which has not been previously reported.

Levi, W. M., Jr., *J. South Carolina M.A.*, 55:94-96, 1959.

for fast, comprehensive relief of hay fever distress

BENADRYL®

ANTIHISTAMINIC-ANTISPASMODIC

You can help your al gic patients to enjoy greate comfort during the hay fever ason by prescribing BENADRYL. *Its potent antihistaminic acti relieves nasal blockage, rhinorrhea, sneezing, itching, and related allergic reactions, hile its atropine-like antispasmodic action suppresses bronchial and gastrointestin spasm.* BENADRYL *Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is vailable in a variety of convenient forms including: Kapseals,® 50 mg. each; Kapseals 50 mg. with ephedrine sulfate, 25 mg.; Capsules, 25 mg. each; Elixir, 10 mg. per 4 cc.; and Emplets,® 50 mg. each, for delayed action. For parenteral therapy,* BENADRYL *Hydrochloride Steri-Vials,® 10 mg. per cc.; and Ampoules, 50 mg. per cc.*

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

CASE REPORT

Twin Pregnancy in a Didelphic Uterus

Twins delivered from a didelphic uterus seldom survive, as in the case presented

W. M. DAWSON, M.D., and W. H. AINSLIE, M.D.,
Metuchen, New Jersey

Congenital anomalies arising from abnormal development or fusion of the Müllerian ducts have long been of interest to doctors generally. Such anomalies often lead to interesting, and at times serious problems in diagnosis and obstetrical management. Uterus bicornis and uterus didelphys do not present serious problems in conception, but such pregnancies are prone to abortion or premature labor. Much rarer is the incidence of twin pregnancies in such anomalies.

A 22 year old girl, gravida one, reported that her last menstrual period had been two months before she was first seen, and her expected date of confinement was set at 7½ months from date. Past history was noncontributory, and examination revealed no apparent abnormalities. Her antenatal course was uneventful until July 3, 1957, when abdominal palpation revealed the probable presence of a twin gestation in a double uterus. This was determined by the presence of a vertical midline groove on the uterus, giving a more or less irregular "U" effect, with a distinct fetal heart in each limb of the "U." These findings were confirmed, and x-ray pelvimetry was ordered to determine fetal size, since the possibility of superfetation was considered after abdominal palpation revealed a seemingly much smaller fetus in the right uterus. Pel-

vimetry demonstrated only a twin pregnancy with each fetus much below term in size, but no significant difference in fetal sizes. The pelvis appeared to be of gynecoid type with ample dimensions.

Labor began spontaneously at 32 weeks of gestation. After a combined first and second stage of two hours (10 minutes after spontaneous rupture of the membranes) the first male twin weighing 50 ounces was delivered by the modified Ritgen maneuver from the right uterus. The placenta expressed five minutes later appeared to be intact. The cervix of the left uterus could be made out, fully effaced and four centimeters dilated, with bulging membranes which were ruptured artificially. Contractions continued irregularly and weakly in the left uterus, and there was some relaxation and bleeding from the right uterus. An infusion of U.S.P. oxytocin, 1:1000, was begun with good results. The second twin, a living male weighing 57 ounces, was delivered from the left uterus by the modified Ritgen maneuver following spontaneous rotation of the vertex from LOA to the OA position. The intact placenta was expressed five minutes later. Subsequent bleeding was minimal and postpartum and puerperal course was uneventful. Both infants survived.

SUMMARY

1. A case is reported of double ovum twins, each twin residing in a separate half of a uterus didelphys.

2. This complication is commonly associated with premature termination of pregnancy.

3. The management of labor and delivery in such a case is illustrated, together with the advantages to be gained by antenatal diagnosis.◀

J.M. Soc. New Jersey, 55:649,1958.

CASE REPORT

Polyarteritis Nodosa

Although the etiologic cause of this disease is not established, infection, allergy, and drug reaction are suggested

FRANCIS J. TENCZAR, JR., M.D., *Chicago, Illinois*

An 80 year old woman entered the hospital because of pain in the hands, shoulders and neck, pedal edema, fatigue, and weakness. Her symptoms began seven months previously with inflammation of the wrists that responded to a course of steroid and salicylate therapy. These agents were less effective when arthritis recurred. One month before admission another exacerbation followed a dental extraction, the ankles, knees and wrists being involved, and there was numbness in the lower extremities and ankle edema. She had lost 10 pounds in the preceding six months, had hypertension without orthopnea or dyspnea, and osteoarthritis for many years.

Abnormal findings were tachycardia, blood pressure 174/100, pedal edema, Heberden's nodes, and dullness, decreased breath sounds, and a few rales over the right pulmonary base. In view of the subsequent course the absence of neurologic signs on admission is important. Laboratory findings included neutrophilia, positive C-reactive protein, and elevated sedimentation rate, increased serum transaminase, and lowered serum albumin. These suggest some nonspecific inflammatory process. X-ray examinations revealed a generalized osteoporosis, multiple old rib fractures, and foci of calcification in the right pleura, infraspinatus tendon, and vessels of the lower extremities.

The patient at first improved with

the use of steroids, a low-sodium diet, and diuretics, but ankle edema recurred. Weakness increased and on the sixteenth hospital day pain was noted in the quadriceps muscles. Chest pain at that time with cough and intermittent fever of 99 to 100 may have been related to a recent fracture of the left third rib.

In the fourth week muscular wasting diminished deep tendon reflexes, there was radial wrist drop and sensory changes, the patient became disoriented, fever increased, rales in the lungs developed and death followed.

The diagnosis falls into the group of collagen diseases.

A diagnosis of polyarteritis is made even though this patient is 80 years of age and a woman. The onset and progression of peripheral neuritis, muscular pain, arthralgia, weakness, fever and failure to respond to steroid hormones all support this diagnosis.

The anatomic diagnoses were polyarteritis nodosa involving heart, skeletal muscle, liver, spleen, pancreas, adrenals, kidneys, intestine, peripheral nerve (left radial), and central nervous system, with recent infarct of the right basal ganglia.

The etiology of polyarteritis nodosa is unknown. Theories include allergy and hypersensitivity, infection, and hypertension. The changes in the tissue are similar to those in allergic and hypersensitivity states such as the Arthus phenomenon, serum sickness and drug reactions. The sulfonamides have been implicated most frequently, but the disease has been reported after administration of penicillin and other antibiotics and after a wide variety of infectious diseases, but no proved etiologic agent has ever been isolated.

Arteritis has been reported following administration of cortisone to patients with rheumatoid arthritis. Four of 14 patients receiving cortisone developed vascular lesions. No instance of arteritis was observed in 38 patients who did not receive cortisone.

Pathologic changes in the renal vessels are encountered in most patients. Clinical symptoms of renal involvement occur in 50 per cent of cases. Abnormal urinary findings—albuminuria, red cells, and casts—are found in 80 per cent of cases.

Illinois M.J., 114:239-244,1958.

Strangulated Femoral Hernia

Of all common hernias, the femoral is most likely to become incarcerated and strangulated. Of 170 patients 116 were women and 54 were men, 71% were between 60 and 90 years of age. Most of the 12 deaths could have been prevented by elective repair. A mass in the femoral ring is the most important physical finding. Intestinal colic with vomiting suggesting acute intestinal obstruction demands careful examination of all hernial orifices. The mortality was low when correct diagnosis was made early. Many patients reached the hospital in profound shock; others had suffered great fluid and electrolyte loss. The excellence of the Cheatle-Henry extraperitoneal retropubic operation is emphasized. Operative mortality among the men was 20%; among the women only 10%. Elective repair of all femoral hernias is strongly advised.

Rogers, F. A., *Ann. Surg.*, 149:9-20,1959.

Raynaud's Disease

Contrary to a common misconception, Raynaud's disease is nonfatal, is usually harmless, and seldom necessitates amputation of digits and never amputation of limbs. Raynaud's phenomenon consists of intermittent changes in color of the skin of the fingers or toes, or both. Usually the digits become white. Cyanosis may develop after the pallor. The phases of cyanosis and pallor result from a temporary spasm in the digital arteries and their branches. After the spasm there may be reactive hyperemia. These color changes lasting a few seconds or a few minutes are usually precipitated by exposure to cold or by emotional stress. Sometimes there is numbness and tingling of the affected digits, but pain is unusual. Although Raynaud's phenomenon is ordinarily confined to terminal portions of the digits, rarely it extends to the hands or feet and affects ears, nose, lips or other exposed parts. Without intermittent color changes in the digits, this diagnosis cannot be made.

All patients with Raynaud's disease have Raynaud's phenomenon; but all patients with Raynaud's phenomenon have Raynaud's disease. The symptoms must be present for two years before the diagnosis of primary Raynaud's disease is considered valid. Seventy-seven per cent of patients with Raynaud's disease are women, the age at onset less than 40 years for 78%. The course is benign. Fewer than 30% of patients have complications—trophic changes, sclerodactylia, and calcinosis cutis. Healing may leave pitted scars or atrophy of distal parts of the digits. Usually complications are not disabling and tend to improve ultimately. They never result in extensive gangrene, and amputation of one or more phalanges is necessary in only 1% of cases. The patient must sometimes be examined in a warm environment, since spasm may render open arteries temporarily pulseless.

Sympathetic reassurance is more important than sympathetic denervation. Detailed instructions about protection of the extremities from heat, cold, and mechanical trauma are sufficient treatment for most such patients. Change in occupation should be done only if the disease is progressive despite other measures. There is no evidence that cigarette smoking has any effect on the course of the disease. In ischemic lesions in the digits, or frequent trouble in spite of protection from cold, whiskey, one or two ounces, three or four times daily, is as effective as any dilator. Ischemic lesions secondary to Raynaud's disease are painful. Narcotics must be used prudently and only for short periods, when milder anodynes fail to permit adequate rest.

Gifford, R. W., Jr., *Heart Bull.*, 8:25-27,1959.

Etiology of Hyperostosis Cranii (Metabolic Craniopathy)

This syndrome is made up of thickening of the inner table of the skull, mainly in the frontal region, and several clinical states such as Stewart-Morel disease, acromegaly, and dystrophia myotonica, and it may occur as senile hyperostosis. Far more women than men are affected. Dystrophia myotonica, a disorder of which hyperostosis cranii is a variable and common feature, occurs equally among men and women. Recent studies have indicated that the causation lies in the endocrine system. The characteristic skull changes in patients examined by the author were a small pituitary fossa, excessive sinus formation, and prognathism. Gonadal atrophy was a common feature, and studies suggested failure of the androgenic function of the adrenals and the testes as the primary feature.

Caughey, J. E., *J. Bone & Joint Surg.*, 40B:701-721, 1958.

Anticoagulants

In patients with a hemorrhagic diathesis, the anticoagulants are contraindicated. Even in polycythemia vera there should be great reluctance to start anticoagulant therapy. Treatment may be necessary for a brief or a long period, or even for life. For the first, heparin is usually selected because it is a more effective antithrombotic agent*. Bishydroxycoumarin has been generally used for long-term therapy. The two agents are used together to start anticoagulation rapidly and shift to chronic therapy without interruption. Because bishydroxycoumarin may take up to 10 days for full effect it is best to continue heparin for this period. Heparin affects the one-stage test (Quick) and one must either utilize another method or perform the test on blood drawn five hours after the last dose. The effects of the drugs used together are not strictly cumulative.

Hemorrhage is infrequent if the patient is kept under close observation. With heparin there is no site of predilection, and, unlike the effect with bishydroxycoumarin, once the clotting time has been elevated to greater than normal, an additional elevation does not proportionally increase the hazard. However, the hazard is increased depending on the duration of the period during which the clotting time is prolonged. When necessary the effects of heparin can be nullified by administration of protamine sulfate given intravenously 1 mg. of protamine to 1 mg. of heparin, effectiveness checked by clotting time, additional given if necessary. Because the effect of heparin is transient, the use of protamine is rarely necessary.

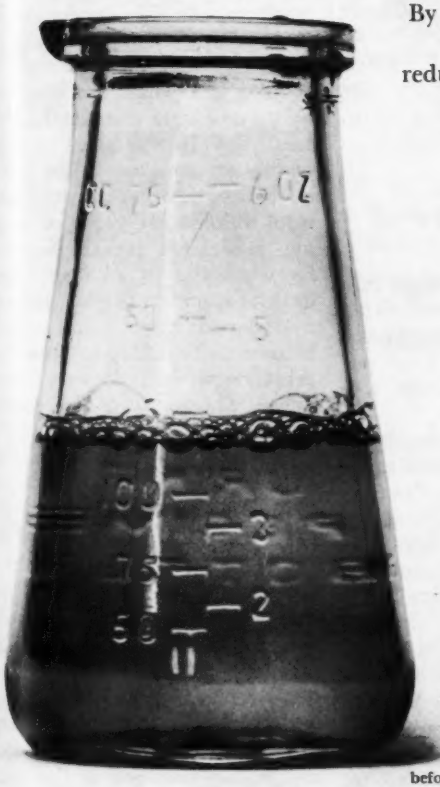
Bleeding during coumarin therapy may be predicted since it generally does not occur unless the clotting time by the one-stake (Quick) method is, or has recently been, less than 10%, occurs in many areas of the body at the same time. An occasional patient will bleed when the "prothrombin" is well above 10%. Look closely for a local reason for bleeding. Some patients seem to improve under therapy though there has been slight effect on prothrombin time. When the "prothrombin" falls to an unsafe level it is usually sufficient

*The distinction between anticoagulant and antithrombotic effect should be noted. The former is measurable *in vitro;* the latter refers to apparent effect on clinical or experimental thrombosis. The two are not necessarily correlated.

urinary discomfort, relieved within 30 minutes

The specific analgesic action of Pyridium provides rapid relief of pain, burning, urgency, frequency. By promoting more normal function, Pyridium reduces the risk of retention and pooled urine.

PYRIDIUM



PYRIDIUM®

brand of phenylazo-diamino-pyridine HCl

provides safe analgesia as long as may be required. AVERAGE DOSAGE: *Adults,* two tablets three times daily before meals. *Children, age 9 to 12 years,* 1 tablet three times daily, before meals. SUPPLIED: Tablets (0.1 Gm. each), bottles of 50, 500 and 1,000.

WARNER CHILCOTT

MORRIS PLAINS, N.J.

complements any anti-infective of your choice

withhold the drug for a day or two, to reinstitute as the "prothrombin" starts to rise. If more urgency exists 5 to 10 mg. of phytonadione, or vitamin K_1, may be given by mouth. In cases in which bleeding has occurred phytonadione may be given parenterally. A 25 mg. intravenous dose will restore the prothrombin time well toward normal within six hours. In cases of extreme emergency the administration of plasma (it need not be fresh) supplies the needed factors immediately.

Newcomb, T. F., *New England J. Med.*, 260:545-548,1959.

Electrolyte Losses From Taking Purges

It is well known that diarrhea may result in excessive loss of electrolytes from the bowel, and that if the intake is not large enough to keep the patient in balance, body depletion will occur.

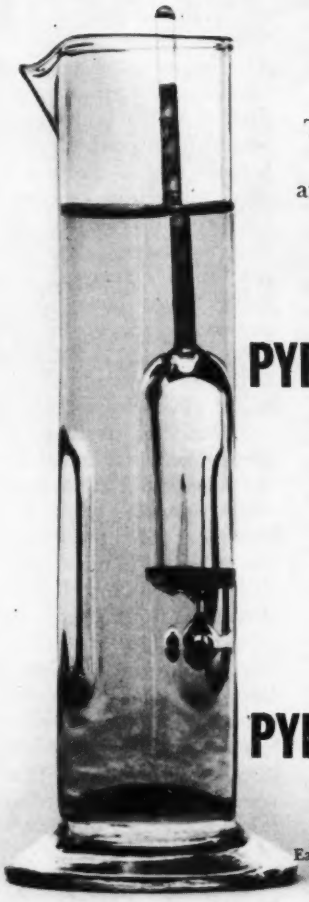
Constipation is the usual explanation for frequent purges. Three cases are described in which chronic purgation caused excessive loss of sodium, potassium, and water in the feces and gave rise to electrolyte-deficiency states. These disturbances were studied by chemical and radioisotope methods. The first patient took purges for 35 years for this reason, and when ulcerative colitis developed she continued taking them to relieve the discomfort of the abdominal distention. The second patient was no more than mildly constipated, but for seven years she desired a purge to relieve rectal symptoms of obscure origin. In the third patient constipation was the only cause for 40 years of purge-taking. Diarrhea resulted from the purges in the second and third patients and was made worse in the first patient. Excessive sodium and potassium lost in the stools produced varying degrees of depletion of the body stores of these substances.

The dietary intake of electrolytes must be reduced to some critical level before an abnormal loss will produce clinical effects. In the first patient the large fecal loss of sodium was compensated over many years by the very high dietary intake. In the second patient the moderate loss of sodium and potassium was balanced by an adequate diet. In the third patient slightly excessive amounts of potassium were lost in the stools, and no doubt the diet covered this loss until the last five years of purge-taking, when the intake became low. Even so, the hypokalemic paralysis did not occur until the end of these five years. It may be that muscles can become acclimatized to potassium deprivation when it is very slowly induced. The hurry of the contents of the large intestine caused by drugs may interfere with the completion of sodium absorption in that organ, and sodium may be lost excessively in the stools. Little is known about the absorption of potassium from the normal colon.

It is of interest to consider whether the purges could have caused the ulcerative colitis in the first patient or the proctosigmoiditis in the second. It is difficult to believe that purges in their usual dosage can produce inflammatory changes in the gut. It is unlikely that the severe colitis in the first patient would have healed even if it had been possible to stop the purges. Aloin was taken by the third patient for 40 years without the appearance of colitis.

Coghill, N. F., et al., *Brit. M.J.*, 1:14-19,1959.

controls acute urinary tract infection and pain



It takes two therapies to assure fullest symptomatic and infection control, and Pyridium Tri-Sulfa provides them both in one Rx for your convenience. The Pyridium component allays the pain, burning, urgency and frequency within 30 minutes ... while the classic triple-sulfa provides prompt therapeutic blood levels, often with the first dose, to control the infection.

PYRIDIUM TRI-SULFA

PYRIDIUM® TRI-SULFA

phenylazo-trisulfapyrimidine

DOSAGE: *Adults*—first day, 2 tablets four times daily. Then 1 tablet four times daily.

SUPPLIED: Bottles of 30 tablets.
Each tablet contains: Pyridium® (Brand of phenylazo-diamino-pyridine HCl) ... 150.0 mg.; Sulfadiazine ... 167.0 mg.; Sulfamerazine ... 167.0 mg.; Sulfamethazine ... 167.0 mg.

WARNER CHILCOTT
MORRIS PLAINS, N.J.

1 tab. q.i.d....rapid analgesia...high sulfa blood levels

Toxoplasmosis

In the congenital form, hydrocephalus is seen in 80% due to obstruction of the aqueduct or of the interventricular foramen on both sides. There are calcifications in half the cases—60 to 70% have chorioretinitis. The same percentage of patients have generalized convulsions. The mental state is always reduced, from the slightest to the greatest degree. Some patients die soon after birth; many have grave defects due to brain and eye injuries; others have few symptoms. The acquired form may present as generalized acute or subacute meningo-encephalitis, febrile or afebrile lymphadenitis, or as monosymptomatic and asymptomatic forms. A man of 60, with a diagnosis of congenital toxoplasmosis, had hydrocephalus, intracranial calcifications, chorioretinitis, history of generalized convulsions soon after birth, and positive dye tests.

Westby, R. K., *Tidsskr. norske laegefor.*, 78:1238-1240,1958.

A New Look at Tuberculin Testing

During the past five years, renewed interest in tuberculin testing as a screening method for tuberculosis case-finding has been stimulated by a variety of factors:

1. The rate of tuberculin reactors in Wisconsin school children has decreased to 5% or less and in University of Wisconsin students to 10%. This makes it more practical to use this test for selecting a highly suspect group consisting of reactors and their household contacts for further investigation.

2. Mobile chest x-ray surveys in the State have become very slightly less productive of tuberculosis in general population groups in recent years. This is due partly to decrease in the rate of active cases, to a greater extent to the fact that certain segments of our population readily accept the chest survey services and are x-rayed and re-x-rayed in succeeding surveys, while another segment—made up largely of older persons, those of lower incomes, and those who believe that they may have tuberculosis—is reluctant to be x-rayed. Special instructional means must be sought to reach these groups; also we believe that a positive, first discovered tuberculin reaction in a child not previously tested, or in a child known to have converted from a nonreactor to a reactor, is an excellent entry to the homes of some of the persons in the group resisting mass x-ray surveys. As a result, it leads to the discovery of active cases which might otherwise escape detection.

3. Periodic testing of selected groups makes it possible to measure the success of control programs.

The availability of drugs for the treatment of tuberculosis increases the value of planned periodic tuberculin testing. Knowledge of the time at which a nonreactor converts to a tuberculin reactor enables the physician to decide whether to institute therapy in the new reactor. For these reasons, the State Board of Health has attempted to stimulate re-appraisal of the value of the tuberculin test, restoring it to full effectiveness in tuberculosis case-finding.

Jensen, A., *Wisconsin M.J.*, 58:170,1959.

Myasthenia Gravis

The easy fatigability and progressive weakness of striated muscle may affect any of the muscles, may be mild or severe, localized or general-

ized. Involvement of the extraocular muscles and the extremities is most common. The pupillary reactions are usually normal. Signs and symptoms involve the bulbar and facial muscles. Many of the patients develop a "myasthenic facies": the facial muscles relax, the nasolabial folds are flattened, the mouth tends to hang open, the lips appear full and the underlip is everted. The patient has difficulty in smiling and whistling, and in attempting to smile the appearance of "snarling" occurs. There may be progressive difficulty in chewing, swallowing and speaking. The neck muscles may be so weakened that the patient has to support his head with his hands. Breathing difficulty may ensue due to weakness of the diaphragm, and the intercostal and accessory muscles. There are no significant physical findings aside from the demonstrations of weakness.

The diagnosis is usually made by careful history, examination demonstrating the characteristic weakness, and pharmacological tests. In 85 to 90% of cases the diagnosis may be established with certainty by the tensilon test (Edrophonuim chloride), now used as a standard test for myasthenia gravis. The test is performed by preparing 1.0 cc. (of a solution 10 mg. per cc.) in a tuberculin syringe and first injecting 0.2 cc. intravenously in 15 seconds. If no reaction occurs after 30 seconds, the remaining 0.8 cc. is injected. If a cholinergic reaction occurs after the injection of 0.2 cc. the test should be stopped and atropine sulfate, 1 mg., administered. The test may be repeated after one-half to one hour using 0.5 or 1.0 cc. The response to tensilon usually occurs within one minute, with definite relief of muscular weakness in a positive result. The reaction is over within 10 minutes.

From 1936 until recently the cornerstone of drug therapy has been the use of prostigmine. Prostigmine has a short duration of action, in severe cases a distinct disadvantage. Overdosage may produce severe general muscular weakness. The therapeutic dose is 15 to 30 mg., three or four times a day orally, to 60 mg. every 3 hours. Some patients have required 60 to 100 15 mg. tablets per day. The dose requirement may be altered by respiratory infections, pregnancy, menstrual periods or emotional stress. Each patient must learn to adjust his own medication. Swallowing difficulty may necessitate intramuscular or subcutaneous use. Atropine may be required for side effects.

Mestinon (pyridostigmine) bromide is preferred now in many clinics. The single dose of 60 mg. correlates with the 15 mg. prostigmine, and has less muscarinic side effects; the duration of action is slightly longer making the drug more useful for night administration. It is more effective than prostigmine in asthenia of the muscles innervated by the cranial nerves. Long-acting tablets of Mestinon are available, having an effect 2½ times that of the regular tablet.

A thymoma requires thymectomy since 25% of these tumors are potentially malignant. The myasthenia gravis remains unchanged.

Cholinergic crisis may require atropine starting with 1.0 mg. of atropine sulfate intravenously or subcutaneously. Respirator care also may be necessary. As much as 8 mg. of atropine have been administered in four hours.

Glaser, G. H., *Connecticut Med.*, 23:213-219,1959.

Hypertension in the Colored and Bantu

Hypertension is known to be common in the Bantu in South Africa. A survey was made among both urban and country Bantu with findings of a significant proportion with blood pressure of over 150/90 in all age groups, though there was a sharp drop in incidence of high blood pressure in males over age 60.

In a survey among both Whites and Negroes in the Southern United States, the average blood-pressure readings, both systolic and diastolic, were higher in the adult Negro than in his white counterpart. All studies support the conclusion that Negroes have essential hypertension, hypertensive heart disease, hypertensive cardiovascular disease or related disorders, more often than Whites.

In Rhodesia, hypertension, both essential and secondary to chronic nephritis, is common. Comparison between the two races was difficult, since the Europeans' expectation of life is much higher.

A study among colored and Bantu in-patients reveals that hypertension and its complications are a common cause of admission and that these cases carry a high mortality. Females are more often affected than males. Renal disease is a common underlying cause. Compared with the European, hypertension presents at a similar age, but is more serious in the female, and the cause of death is more evenly distributed between heart failure, cerebrovascular accidents, and uremia. Electrocardiographic changes are found commonly even among the milder cases.

Fraser, B. N., *Brit. M.J.*, 1:761-764,1959.

Cerebrospinal-Fluid Culture in Multiple Sclerosis

Over some six years spirochetes have been found in sections of central-nervous-system tissue of persons dying with this disease. Some have maintained that what were described as spirochetes were staining artifacts. In more recent years spirochetes have been found on microscopical examination of tissues obtained at autopsy and stained with a special silver-impregnation technic. In 1957 spirochetes were found in the spinal fluids of patients with multiple sclerosis by the use of dark-field microscopy. In the same month a report appeared in this country of the successful cultivation of spirochetes from the cerebrospinal fluid of 59 (78%) of 76 patients with multiple sclerosis by the use of a specially prepared culture medium.

In a recent investigation it was impossible to isolate spirochetes from the cerebrospinal fluid of 32 patients with multiple sclerosis. Cultures were observed for two to six months. Personal communication between investigators carrying on similar studies reveal a common inability to reproduce the results reported previously. This may be due, in part at least, to difficulties in preparing the medium.

In the finding of positive cultures for spirochetes in the cerebrospinal fluid of a high proportion of patients with multiple sclerosis is eventually verified, a problem still requiring solution would be whether the presence of such organisms had any bearing on the pathogenesis of the lesions of multiple sclerosis.

Mavor, H., et. al., *New England J. Med.*, 260:860-863,1959.

Hemodynamic Effects of Atrial Fibrillation in Patients with Mitral Valvular Disease

These effects were studied in 80 patients with mitral valvular disease, 30 of whom had atrial fibrillation, 50 sinus rhythm. Pulmonary pressure was lower in patients with atrial fibrillation. The discrepancy in pulmonary arterial pressure with atrial fibrillation of "groups 1 to 4" was also less than among patients with sinus rhythm. No patient with atrial fibrillation had a capillary pressure above 25 mm. Hg. The degree of dilation of the left atrium in patients with atrial fibrillation was greater than in those with sinus rhythm. It relieved the pulmonary hypertension but increased hypertension in the right atrium and in the venous systemic circulation.

Caini, B., & Brunori, M. M., *Sett. med.*, 46:395-401, 1958.

Flumethiazide as an Adjunct to Hypertension Therapy

Since further examination of diuretic agents has revealed antihypertensive properties, a number of agents have been studied for this attribute. The latest of these compounds is flumethiazide (6-[trifluoromethyl]-1, 4,2-benzothiadiazine-7-sulfonamide,1, 1-dioxide). The clinical pharmacology and results of the use of the drug in the treatment of edematous states of varied etiology indicate that flumethiazide has a potency as a diuretic not significantly different from that of cholorthiazide. Tolerence to the compound does not develop and there is no evidence that it produces more side effects than chlorothiazide or the mercurials.

Thirteen patients were receiving chlorothiazide in addition to rauwolfia 100 mg. twice daily. Another 12 were receiving chlorothiazide in addition to rauwolfia, 100 mg. twice daily, and mecamylamine in dosages to control hypertension. Flumethiazide in equivalent doses was substituted for chlorothiazide, and the patients were observed at three, six and 12 weeks for evidences of beneficial or adverse reactions.

Another 25 patients on rauwolfia alone for the control of mild hypertension without edema, were given flumethiazide 0.5 gm. twice daily, additionally, and observed at similar intervals.

Flumethiazide appears to be equipotent to chlorothiazide in ability to maintain blood-pressure reduction achieved with therapy by chlorothiazide, rauwolfia and mecamylamine, and capable of satisfactorily reducing blood pressure when it is added to rauwolfia therapy alone.

Montero, A. C., et al., *New England J. Med.*, 260: 872-873,1959.

briefs: SURGICAL

Intra-Articular Injections in Osteoarthritis of the Knee

Of 59 men and 122 women with osteoarthritis of the knee treated by intra-articular injections all failed to show subsidence on previous treatment and presented positive x-ray evidence of osteoarthritis. The 3 solutions employed for injection were lactic acid solution, procaine, hydrochloride, and hydrocortisone. Isotonic sodium chloride and mock injections were used as controls. Each patient was allotted 1 of the 5 types of injection at random, this continued throughout the treatment, 5 injections at intervals of 2 weeks. Each patient had 2 re-examinations, 6 weeks and 6 months after the end of the treatment. Irrespective of the type of injection used, including the controls, no significance in the effects was demonstrable. There was objective improvement, fairly evenly distributed. Presumably, this indicates the more natural and confident use of the joints and is a reflection of the outlook of the patient after the injection. The men and the assessor agreed almost completely; more women expressed satisfaction than the assessor could accept on clinical grounds. If injections are to be made into such joints, the least noxious and cheapest substance (or mock injection) should be used.

Miller, J. H., et al., *J. Bone & Joint Surg.*, 40B:636-643,1958

Uses and Abuses of Blood Transfusions

Lack of positive indication is the most important contraindication to the use of blood; benefits to be anticipated should outweigh the hazards and costs of transfusion therapy, and full knowledge and concern that maximal benefits will result only if the material transfused is that which best supplies the patients need. Three-week-old bank blood is satisfactory for blood replacement during surgery or following trauma; blood stored for only a short time is better for patients whose marrow is not producing red cells at a normal rate and who will require transfusions over a long time. If the indication is replacement of red cells, in bone-marrow failure or in the management of certain types of hemolytic anemia, the use of separated red cells is valuable therapy. The plasma from which the red cells have been separated may be used in the treatment of shock or hypoproteinemia and of certain hemorrhagic disorders, either as the whole substance or after fractionation into its protein components.

The processing of albumin, gamma globulin, fibrinogen and other factors provides replacement therapy for specific deficiencies in selected patients. The use of platelet-rich plasma has prevented bleeding from certain patients with thrombocyto-

penia, and fresh-frozen plasma is invaluable in the treatment of hemophilia. Red cells from which the plasma has been removed can do great good to patients who could not endure added plasma.

Transfusion reactions may take the form of fever, chills, bleeding manifestations, urticaria and, occasionally, death from sepsis. Hemolytic transfusion reactions result from incompatibility between the donor's and recipient's blood. Serum hepatitis from virus in the transfused whole blood or plasma is a risk inherent in any transfusion. Transfusion hemosiderosis is unavoidable in patients with bone marrow failure depending upon transfused blood for the maintenance of their existence.

Give transfusions only as specifically indicated. Development of transfusion polycythemia happens in the patient who has been given "tonic" or "cosmetic" transfusions in order to make his physician feel better, but which have nothing but an adverse effect upon the recipient. A patient with a debilitating disease, confined to bed, or in restricted activity does not require a hemoglobin level of the normal healthy young adult. The patient who requires only one transfusion as part of the medical treatment probably would get along better without that one. The giving of whole blood or blood components to patients with advanced malignant disease or with anemias which can and should be treated with iron or vitamin B_{12} is fraught with danger to the patient. The masking of an underlying anemia by transfused blood often delays or makes impossible accurate diagnosis.

Loeb, V., Jr., *Missouri Med.*, 56:399-401,1959.

Common Bile Duct After Cholecystectomy

The common bile duct rarely becomes further dilated after cholecystectomy. The theory that some post-cholecystectomy symptoms are the result of an increasingly distending duct would, therefore, appear to have no basis in fact. The question arises as to the cause of the dilation: is it merely the presence or passage of stones, or is co-existing spasm or fibrosis of the sphincter of Oddi a major factor? It would be interesting to know whether those ducts with residual stones after cholecystectomy tend to dilate further.

A study of the possibility of inaccuracy due to the injection of fluid into the duct during the operative cholangiography has been made by taking pre-operative x-rays at varying degrees of hydrostatic pressure in the common bile duct. Two skiagrams are done; one at the pressure where the sphincter of Oddi opens (usually about 10 to 15 cm.), the other at 40 cm. pressure. The films so produced are directly comparable, as they are both taken at an interval of a few seconds with an over couch tube at a fixed distance. This makes it possible to give an accurate estimate of the distensibility of the duct at varying pressures.

Assessing 39 recent consecutive cases, 13 were found with an average pressure rise of 21.8 cm. water without increase of diameter of the duct. In the remaining 26 cases with an average pressure change of 28 cm. water there was an average increase of 1.7 mm. No significance can be attached to apparent alterations in duct size of 2 mm. or less. It would seem, therefore, that inaccuracies are unlikely from this source. From the survey of a large number of these pre-operative cholangiograms, it is suggested that 10 cm. to 11 cm. should be taken as the upper limit of diameter of a normal duct.

Caper, W. M., & Gall, W. J., *Brit. M.J.*, 1:973,1959.

The Management of Pathological Fracture of the Major Long Bones from Metastatic Cancer

Of 40 patients (29 women, 11 men) with disseminated cancer, 33 had pathological fractures of the long bones which were treated by internal fixation and irradition, and 7 were given the same treatment for "prophylaxis," since they had destructive lesions of the long bones from cancer metastases. Of the 43 lesions the neck and trochanteric region of the femur was involved in 19, the upper third of the shaft of the femur in 10, the middle third in 8, and the humerus in 6. All were treated by internal fixation at the earliest opportunity, either by use of an intramedullary nail or by nail and plate. All were given irradiation, and in cases of intermedullary fixation the whole length of the bone was irradiated. Excluding those treated prophylactically, 25 of the 30 with fracture of the lower extremities survived for 6 weeks or more and all returned to walking with crutches; union took place in 80% of the fractures. Four of the 5 with fracture of the humerus regained a useful arm. The prophylactic internal fixation and irradiation appeared helpful in 5 of the 7 patients. Internal fixation might not be justified in treatment of a single metastasis from a primary low-grade cancer, but, in general, the theoretical dangers of dissemination may be ignored.

Bremner, R. A., & Jelliffee, A. M., *J. Bone & Joint Surg.*, 40B:652-659,1958.

briefs: THERAPEUTIC

A Hand-Operated Resuscitator

In the first-aid treatment of respiratory failure from any cause, speed in applying artificial respiration is essential. Any form of ventilation, manual or otherwise, may be life-saving if it is applied at once, and there is a growing view that positive pressure, either in the form of mouth-to-mouth or by machine, is more effective. Possibly because of esthetic considerations, the mouth-to-mouth method has never achieved the popularity it deserves, and although many positive-pressure machines are now available, most of them can be operated only by trained medical personnel. These are complicated and cumbersome because they need oxygen cylinders for operation.

The ideal machine should be simple, portable, and robust, cheap to manufacture, and so designed that it can be used by untrained personnel. A simple hand-operated resuscitator which appears to meet all requirements has been developed. It consists of three main components: a rubber facepiece, an exhalation valve unit and an air supply unit. All the metal parts are anodized aluminum, and all the rubber parts are of high quality with a life expectancy of at least 10 years. The components are connected by screwed joints so that they can be disconnected for cleaning. The whole apparatus can be sterilized by autoclaving or by boiling.

The resuscitator weighs just under two pounds and is contained in a rigid box, 10 x 6 x 6 inches, with a carrying-handle. Inside the lid of the box are the instructions for use of the device.

This device has been thoroughly tested during the past eight years, both experimentally and clinically, on a large number of unconscious subjects under widely varying climatic conditions and has been found to be entirely satisfactory. It has been used successfully in patients with poliomyelitis who were transported by air for emergency resuscitation in hospital wards, and by hospital orderlies previously untrained in its use. It has also formed part of a controlled study on artificial respiration.

Lucas, B. G. B., et al., *Brit. M.J.*, 1:1165-1166,1959.

Nonverbal Approach in the Treatment of Neurosis

The nonverbal mode may prove to be the basic ingredient in the management of neuroses. Eleven reports by different investigators over a period of 20 years found improvement in 55 to 87%, an average of 67%. No one approach to psychiatric disorder can claim a monopoly upon wisdom, understanding or therapeutic efficiency. Most psychodynamic therapy is applied to patients of the upper and middle classes, while psycho-neurotic persons of lower

class are most likely to receive only supportive and manipulative psychotherapy. The difference is not due only to economic reasons but also to difficulties in communication between the psychiatrist and the lower-class patient. The general practitioner, more accustomed to dealing with patients of all classes, may be better able to bridge the gap, both verbally and nonverbally.

The history should be unhurried, the patient's strain thus given a chance to subside. The permissive approach is not always best; firmness may be more effective, but the physician's basic attitude should be compassionate, never moralistic or prejudging. Only if the patient feels that he can trust the physician will he talk freely, thereby giving the therapist an opportunity to collect the facts. The patient is encouraged to tell his story, thereby unburdening himself of his troubles. Such an emotional release is sometimes all that is required, but in other instances it will at least indicate his readiness to accept constructive measures and suggestions.

Attention must be given to every seemingly unimportant detail, not only *what* symptom the patient complains about, but *how* he does it. Simple questions as to age, family status, occupation, general health and former diseases often bring forth answers which reveal the degree of adjustment to essential life situations. From all these data and the patient's general appearance and manner the physician may form an impression of his personality, the seriousness of his condition, and his accessibility and his insight into his problems. On these findings the physician will decide how best to manage the case or whether a psychiatric consultation might be indicated.

One of the greatest advantages of these nonverbal methods is that it becomes possible to weave psychotherapy unobtrusively into other consciously acceptable treatment methods, thereby enlarging the range of communication. The immediate aim is relief of symptoms, and only time can tell what further benefits will accrue to the patient. The general physician can make an important contribution by helping the patient to use his own recuperative powers for a fresh start toward better mental health.

Batten, C. T., *California Med.*, 90:202-206,1959.

Sulfadimethoxine: Clinical Appraisal in 120 Patients

The use of sulfadimethoxine (Madribon) in 120 patients with various upper respiratory tract, urinary tract and soft tissue infections previously treated unsuccessfully with wide spectrum antibiotics produced an excellent response in 88 per cent. The types of infection included streptococcal pharyngitis, meningitis, and furunculosis caused by resistant staphylococci. Initial dosage ranged from 1 Gm. in adults to 125 mg./20 lbs. of body weight in children. Maintenance dosage was 0.5 Gm. daily in two-thirds of the patients and 1 Gm. in the remainder. Treatment was continued for periods of from four to seven days.

Results in hospitalized patients were evaluated according to blood and urine findings, cultures, and sensivity studies. Non-hospitalized patients were evaluated according to evidence of leukocytosis and toxemia. When indicated, analgesics, anti-

pyretics, expectorants, and abscess incision and drainage were employed. Although toxic effects such as nausea, vomiting, diarrhea and dermatitis were especially looked for, none occurred. The only side effect noted was slight headache in one patient previously found sensitive to sulfonamides.

In a family group of two parents and three children, all with recurrent and resistant furuncular lesions of the face, previous therapy with several commercially available antibiotics was unsuccessful. Treatment with sulfadimethoxine brought dramatic improvement in all five without evidence of allergic reactions, even though three of the patients showed a definite allergic history.

Leming, B. H., Jr., et al., *Antibiotic Med. & Clin. Therapy*, 6:32-39,1959.

Inorganic Arsenic

Inorganic arsenic, in the form of Fowler's solution, is the only dependable remedy for lichen planus, a distressing skin condition which, at least here (Kenya), seems to be getting more common among all races. Given judiciously, and discontinued at the slightest sign of intolerance, it is safe and successful remedy. Organic arsenic compounds are much more dangerous. Several cases of fatal dermatitis have occurred after neoarsphenamine and similar preparations, but an arsenical dermatosis or a cutaneous cancer due to metallic arsenic has not been seen. Of 240 patients suffering from cutaneous cancer treated, not one gave a history of previous prolonged arsenic medication. Inorganic arsenic has also been recommended as a remedy for psoriasis.

Piers, F., *Brit. M.J.*, 1:651,1959.

briefs: OBSTETRIC

The Incompetent Cervix in Repetitive Abortion and Premature Labor

It has been suggested that inability to retain an otherwise normal pregnancy to a stage of viability may be due to an anatomic defect in the internal os of the cervix, or the entire cervix is incompetent. The lesion is said to be identifiable by x-ray after the introduction of a small balloon containing radiopaque substance into the lower uterine cavity. The procedure for the repair of the defect is designed for the nongravid uterus. When seen, the majority of these patients are pregnant. The history usually is that the first and sometimes the second pregnancy proceeded to, or near, term, but later a series of nonviable pregnancies occurred. An occasional patient has never had a pregnancy reach the stage of medical viability.

The cervix dilates without discomfort, over a period of days or possibly weeks, to the point where the membranes are visible on speculum examination. Unless this is recognized early, the membranes will rupture and the pregnancy will end prematurely. Endocrine therapy alone has not sufficed, but more encouraging results are being reported when it is combined with surgical therapy.

In one clinic the anesthetized patient is placed in moderate Trendelenburg position, the exposed cervix is grasped with DeLee cervical tenacula, and a 1 cm. transverse incision made in the vaginal mucosa overlying the posterior surface of the cervix. The mucous membrane of the anterior cervix is then incised transversely as in vaginal hysterotomy and the bladder is displaced upward away from the cervix. Each end of a polyethylene-tube suture, measuring 0.067 inches in outer daimeter, containing a woven steel wire, size 0, and threaded on a large half-circle needle, is passed through the posterior incisions beneath the vaginal mucosa as close to the cervix as possible to emerge anteriorly. A finger in the cervical canal helps guide the needle and avoid perforation of the membranes. One or two additional sutures are similarly placed nearby, usually distal, but sometimes above the first suture. The sutures are tied and, to avoid their downward displacement by contraction, transfixed to the cervix fore and aft with silk sutures which are loosely tied, forming a small loop to facilitate subsequent removal of the polyethylene suture. The anterior and posterior incisions in the mucosa are closed, and this simple procedure is completed. The patient is given 300 to 500 mg. of progesterone daily until the sutures are removed. A broad-spectrum antibiotic is administered during the hospital stay, and the patient is dis-

Novahistine works better than antihistamines alone

Stuffy, runny noses...swollen, weepy eyes are more effectively relieved with Novahistine. The distinctly additive action of the vasoconstrictor and antihistamine combined in Novahistine relieves allergic symptoms more effectively than either drug alone.

one dose of 2 tablets for day-long or night-long relief.

Each long-acting tablet contains Phenylephrine HCl 20 mg. and Chlorprophenpyridamine maleate 4 mg.

Bottles of 50 and 250 green, film-coated tablets.

PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc., Indianapolis 6, Indiana

Novahistine LP* LONG-ACTING

*Trademark

charged on the fourth postoperative day on a restricted regimen.

One patient with a badly lacerated cervix was carried through pregnancy with the use of this technic, after a failure that followed a fascia lata repair. Thirteen of the 18 patients had been delivered, with 10 infants surviving. Of the five undelivered, two are beyond the 34th week. Eight patients were operated on between the 16th and 20th, two from the 21st to the 24th, five from the 25th to the 28th week. Two of the three remaining patients were operated on at the 29th week and one at the 30th. The last three patients all demonstrated bulging membranes through a cervix dilated to at least five cm.

Most of these patients were ambulatory by the third postoperative day and gradually assumed increased activity. Three patients had to limit their activity strictly since exertion of the mildest degree brought on painful uterine contraction. The remainder were able to return for prenatal examinations and to carry on normal activity.

Three of the 13 patients were delivered by the abdominal route, the remaining 10 by the pelvic route after removal of the suture.

Easterday, C. L., & Reid, D. E., *New England J. Med.*, 260:687-690,1959.

Prenatal Care

In many communities expectant fathers and mothers are instructed in classes subsidized by the Red Cross, local health departments, some even by medical societies and nursing associations. Class teaching in elementary anatomy and physiology, hygiene and nutrition, and baby care can serve good purposes. Some believe that all such instruction can best be done individually by the doctor.

Today most women expect prenatal care. In these few months, if the doctor is willing, he can recognize and have treated dental caries, lues, pulmonary tuberculosis, and emotional disorders, and vaccinate against poliomyelitis. One occasionally discovers cancer of the breast or cervix. The Papanicolaou smear is as important as the Kahn test.

Many appraise adequate feeding on the basis of the individual's sense of well-being, her ability and capacity to function properly and lack of evidence of nutritional disturbance. Common sense will include attention to one's likes and dislikes. There is no laboratory standard of nutritional deficiency, except in almost terminal stages. For the past 25 years most of us have emphasized the importance of a high-protein diet during pregnancy. A low-sodium diet is urged.

A weight gain during pregnancy of 15-20 pounds is desirable. It may be that underweight patients should gain more, the overweight gain less. A diet affording 2600 calories per day should be adequate. Counting calories or making a ritual of the meal is not the aim. A vareity of minerals and vitamins is needed. *No supplemental minerals* if the patient has been on a normal diet. A pint of milk per day will give 1.2 mg. of calcium, close to the maximum calculated for late pregnancy and certainly more than is needed during the first five months. Meat and vegetables provide additional calcium. The next time a patient complains of leg cramps, give her one of the aluminum hydroxide preparations rather than more milk. You will be happily surprised.

Butazolidin

(phenylbutazone

tablets · alka capsules

potent · nonhormonal · anti-inflammatory ag

BUTAZOLIDIN tablets or the Alka capsules are **equally effective but individually adaptable in a wide range of arthritic disorders.**

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases...over half, 50.7 per cent showed at least major improvement, with 21.8 per cent showing minor improvement...."[2] **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...."[2] **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement...."[2]

References: 1. Graham, W.: C... M. A. J. 79:634 (Oct. 15) ... 2. Robins, H. M.; Lockie, L. M.; ... cross, B.; Latona, S., and Ri... D. J.: Am. Pract. Digest T... 8:1758, 1957. 3. Kuzell, W. C.; ... farzick, R. W.; Naugler, W. E.; ... Champlin, B. M.: New Engl... Med. 256:388, 1957.

Availability BUTAZOLIDIN (p... butazone GEIGY): Red coated ... of 100 mg. BUTAZOLIDIN ... Capsules containing BUTAZOL... (phenylbutazone GEIGY), 20... dried aluminum hydroxide ... 100 mg.; magnesium tri... 150 mg.; homatropine me... mide, 1.25 mg.

geig

ARDSLEY, NEW

Most pregnant women evidence an iron deficiency anemia. As a safeguard against blood loss during labor and to provide the fetus with its needs, supplemental iron is often required. Ferrous sulfate, gr. 3 t.i.d., is generally sufficient. At times trace elements like cobalt favor absorption and utilization of iron. Folic acid, ascorbic acid and vitamin B_{12} are indicated in the treatment of megaloblastic anemia only.

The traveling of pregnant women has no bearing on abortion or prematurity. Automobile travel may lead to difficulties in a strange locality, but today good care is to be had most everywhere. If travel leads to nausea, thorazine or dramamine is of great help. It is doubtful if the time of the month has any bearing on abortion or early labor.

No one could object to showering. For those who enjoy soaking, what harm can come?

Some increase in local secretion is physiologic, associated itch or odor suggests trichomonas or yeast vaginitis. Treat the same as the non-pregnant. No form of insufflation or douching. Yeast suggests incipient diabetes.

The primary concern is with rubella, and only during the first three months of pregnancy. If the patient has been definitely exposed to german measles, has never had the disease, and is in the first trimester, give her 20 cc. of gamma globulin prophylactically.

The determination of the Rh reaction of the mother's blood should be a standard office procedure. If the reaction is negative, we must know whether the blood contains antibodies—a hospital or large laboratory procedure.

DeCosta, E. J., *J. Oklahoma M.A.*, 52:69-74,1959.

Doctors and the Law

A continuing series of articles discussing actual cases involving medico-legal problems of interest to all practicing physicians

CHARLES J. FRANKEL, M.D., LL.B., *Editor*

▶May a malpractice action, based on the leaving of Kelly forceps in the patient's abdomen, be submitted to jury under doctrine of res ipsa loquitur, where there is medical evidence it would not have been good practice to have searched the operating area?◀

This issue was presented to a U.S. District Court in 1958 (*Swanson* vs *Hill*, 166 F. Supp. (N.D.) 296). Defendants performed a serious abdominal operation on plaintiff. The operation itself was successful. However, for some time after the operation, plaintiff suffered pain. About fourteen months after the operation, other doctors, by means of x-rays and examination, discovered Kelly forcepts in her abdomen and removed them.

Plaintiff's action is based solely on damages suffered because of defendants' failure to remove the forceps from her abdomen. The case was submitted to the jury under the doctrine of *res ipsa loquitur*. Defendants argued that to so submit the case was improper because the doctrine is applicable only in the absence of an explanation by defendants. Defendants, and other doctors testifying for them, stated that good surgical practice dictated that no search be made in the abdomen above the incision's site for fear of adding shock and trauma to plaintiff's already serious condition and that all surgical procedures, practices and methods used, includ-

ing not searching the upper abdomen and intestines, were practices accepted and approved by the profession in the community where the surgery was performed. The Court said that, admitting that an ordinary exploration for instruments or other foreign bodies could not have been made at the operation's end, because of plaintiff's physical condition, one need not be a surgeon to suggest that professional prudence would have indicated a post-operative x-ray and examination in the area of surgery. Therefore, defendants were negligent and answerable for damages caused by leaving the forceps in plaintiff's body and the case was properly submitted to the jury under the doctrine of res ipsa loquitur.

►Is clause in partnership contract, barring doctor, upon dissolution of partnership, from practicing within radius of 30 miles of town where partnership was located, valid?◄

This question was before the Court of Common Pleas of Trumbull County, Ohio, in 1955 (*Droba* vs *Berry*, 139 N.E. (2d) 124). Defendant, who had an established practice in Kinsman in Trumbull County, took plaintiff, who had just completed his internship, into partnership so that there would be someone to look after the practice while he was in service. As a part of the partnership agreement, plaintiff agreed that, in the event of its dissolution, he would not practice within a radius of 30 miles of Kinsman.

The Court said a doctor may agree to restrict himself in the practice of his profession. In order for such an agreement to be valid it must be reasonable. Whether such an agreement is reasonable is to be determined by considering whether the restraint is only such as to afford fair protection to the interests of the party in whose favor it is given and not so large as to interfere with the interests of the public. The question of reasonableness must be determined on the facts of the particular case.

A doctor residing in Kinsman would naturally expect to draw his patients from the town and the surrounding area. Within a range of 8-14 miles, in various directions, are other small towns where a number of doctors are located with whom defendant is in competition. Within a radius no more than 30 miles from Kinsman are the Mahoning and Shenango Valleys, which include the populous and industrialized cities of Warren and Youngstown. Throughout these areas many doctors are practicing and many hospitals are maintained. The Court said that, considering the comparatively large number of doctors practicing only slightly more than 10 miles from Kinsman, and the great need of doctors by those living in the highly industrialized Mahoning and Shenango Valleys, defendant could not reasonably claim that these doctors are competing with him for Kinsman, nor could these doctors claim that defendant was competing with them for any portion of the industrialized territory within 30 miles of Kinsman. Describing the situation on which defendant must rely for the validity of the 30 mile restriction clearly demonstrates its unreasonableness and it is, therefore, void.

►Is a regulation which applies to private proprietary hospitals, but not to public and voluntary nonprofit hospitals, violative of the constitutional right to equal protection of the laws?

Is regulation requiring a minimum floor area for each bed unreasonable?◀

The New York Court of Appeals had these questions before it in *Engelsher* vs *Jacobs*, 184 N.Y.S. (2) 640 (1959). The Board of Hospitals of New York City denied the plaintiff a license to operate a private proprietary hospital because he had not complied with new regulations of the New York City Hospital Code. The new regulations require that, in other than private rooms, each bed must have a floor area of 70 square feet. As to private rooms, hospitals licensed before 1956 were to have this same minimum floor area, while those licensed thereafter were to provide a floor area of 100 square feet. The regulations also required an increase in the nursing staff of private proprietary hospitals.

Plaintiff contended that, since the regulations applied to private proprietary hospitals, but not to public hospitals and voluntary nonprofit hospitals, they violated the constitutional right to equal protection of the laws. The Court said that the police power of the State is the least limitable of all governmental powers. Hospitals are indisputably subject to the exercise of the police power because they are institutions dealing directly with the health of the citizenry. Under the New York City Charter the Board of Hospitals is authorized to promulgate necessary rules and regulations for private proprietary hospitals to promote the public health and welfare. The legislature has thus established such hospitals in a special class. All private proprietary hospitals are treated alike under the regulations in question. Equal protection is accomplished when all of the same class are treated in a like manner. There is no violation of the equal protection clause if one class is treated differently than other classes. The Court further pointed out that there was no evidence in the record to indicate that there are no similar regulations in statutes or rules applicable to public hospitals or voluntary nonprofit hospitals.

Plaintiff further contended the regulations were unreasonable. The Court said they were undoubtedly designed to promote the health and welfare of the public generally. In an opinion in an earlier case involving similar regulations, there is a suggestion that expenditures incurred in order to comply with the regulations must be reasonable in order for the regulations to be valid. Here the minimum space requirements can easily be met by removing one or more beds from rooms containing two or more beds; the main loss is the loss of future profit. The Court said it could not say that the minimum space requirements are unreasonable as a matter of law. Therefore, the refusal to issue plaintiff a license, because of failure to comply with the regulations, was not arbitrary.

►In an action for injuries resulting from dislodgment of two of patient's teeth during administration of anesthetic, may the question of anesthetist's liability for malpractice be submitted to jury even though the patient presents no expert evidence of anesthetist's negligence? Is surgeon who performed the operation liable because of alleged indifference to patient's condition after being told the teeth were dislodged when the anesthetic was administered?◀

These questions were passed on

by the Florida Supreme Court in *Dohr* vs *Smith,* 104 So. (2d) 29 (1958). The anesthetist, after first putting the patient to sleep with sodium pentothal, inserted an "airway" into the windpipe, using a laryngoscope. While doing this the anesthetist heard a faint noise like the cracking of glass. She then removed the laryngoscope and examined the patient's mouth visually and with her hand. The facing of a tooth came loose and fell into her hand, a peg for a tooth was revealed and a vacant space next to the peg was discovered. When the operation was completed the anesthetist told the surgeon that one of the patient's teeth had disappeared during administration of the anesthetic; the surgeon took no action in the matter. The next day, the patient, upon seeing the facing recovered by the anesthetist, told her more was missing and that the bridgework consisted of two teeth. She informed the surgeon of the situation. Neither the surgeon or the anesthetist made any effort to locate the missing teeth; they assumed the patient had swallowed them. Shortly thereafter, the patient developed an "unproductive" cough and this was noted by the surgeon on the hospital record. However, no x-rays were taken in an effort to locate the missing teeth. Several weeks after the operation, the anesthetist, who was apparently still apprehensive about the missing teeth, called on the patient and suggested they might be lodged in her lung. X-rays were then taken, and the two teeth, one lacking a facing, were located in the right bronchus. They were removed by bronchoscopy procedure by another doctor.

The anesthetist had visited the patient the day before the operation to determine her fitness to undergo it. She testified she examined the patient's teeth, because it is routine, in giving anesthetics, to be sure that a patient has his teeth and that if he has a plate to take it out. She got the impression the teeth were all right and it never occurred to her that the two front teeth were false. She testified she refrained from asking the patient if any of her teeth were false because the question would have been insulting.

The anesthetist contended that the issue of her negligence should not be submitted to the jury because the patient presented no expert testimony that she had been negligent. The Court said the patient's action against the anesthetist should not be defeated simply because she failed to present expert testimony that the anesthetist had been negligent. The very caution the anesthetist exercised in making a routine examination of the patient's teeth undermines her position. The jury could reasonably find, on the basis of common knowledge and experience, regardless of expert testimony, that the patient needlessly suffered from a condition the anesthetist herself tried to prevent.

The basis of the claim against the surgeon is his alleged indifference when informed the teeth were missing. There was evidence indicating he was not indifferent to the patient's condition. Several days after her release from the hospital, he made an appointment for her for chest x-rays which she cancelled. He knew the anesthetist was keeping informed of the patient's condition. The surgeon was faced with the question of whether the patient would be injurious

affected if he excited her immediately after the operation by suggesting the teeth might be embedded in one of her lungs. The Court said that ordinarily the conflicting evidence as to the surgeon's indifference would be submitted to the jury but that it should not be in this case because there was no expert testimony as to what other surgeons in the community would have done or what course of treatment different from the surgeon's they would have followed. The facts surrounding his conduct were not so simple or obvious as to place him in the same category as the anesthetist.

►Under Internal Revenue Code, may doctor deduct, as business expense or expense for maintenance of income-producing property, sums expended as legal fees in defense against charges of income tax evasion?◄

This question was passed on by the U.S. Court of Claims in 1958 (*Port* vs *United States*, 163 F. Supp. 645). Plaintiff, a California doctor, was, after two trials, convicted of willful evasion of federal income tax laws. He expended $20,750 in attorney's fees in defending against the charges. Following his conviction, the California Board of Medical Examiners, acting under its statutory powers, suspended his license for thirty days and placed him on probation for three years.

Plaintiff argued that the attorney's fees should be deductible as ordinary and necessary business expenses, because conviction of the crime charged could result in revocation of his medical license, thereby destroying his "business" entirely. The Court said deductibility of expenses depends, not upon a transaction's effect on one's business or income-producing property, but on its cause and turns wholly upon the nature of the activities to which it relates. Whether plaintiff's legal expenses are deductible depends on whether they proximately resulted from and directly related to his "business" or maintenance of income-producing property.

The Court said the expenses incurred were not made necessary by the nature of plaintiff's business. The proceedings were not an attack on plaintiff's business, did not seek necessarily to destroy his business and did not arise from a criminal characterization of his business practices. The expenses which plaintiff seeks to deduct were incurred in defense of a criminal charge against him as an individual to impose personal punishment. Conviction of the charge could, it is true, effectively deprive him of his business for a long period of time and could, indirectly, if the punishment were sufficiently severe, deprive him of all or substantially all of his income or income producing property. However, this does not mean that the expenses were proximately caused by his business or his management of property. The expenses were proximately caused by, and most directly related to his personal wrongdoing and cannot, therefore be characterized as "business" expenses and deducted.◄

The Doctor Builds His Estate

Prepared for the readers of Clinical Medicine by the Research Department of the leading investment banking and brokerage firm of Bache & Co., 36 Wall Street, New York 5, New York

These monthly articles point out one method by which the professional man may overcome the particular handicap imposed upon him by our tax structure, which taxes the bulk of his income at normal income tax rates, as opposed to the capital gains tax avenue open to many business men. One solution to this problem is the systematic investment of a portion of current income each year in securities. Such a program, which should include many different types of investments such as bonds, preferred stock, common shares and shares of mutual funds, will have as its objectives growth of principal together with reasonable income. We again emphasize that even the most complete series of articles of this type cannot take the place of consultation with a representative of a reputable brokerage firm.

Although there can be no advance evaluation of the outcome of the forthcoming exchange of visits between President Eisenhower and Premier Krushchev, many investors interpreted the announcement as foreshadowing an easing of the cold war tensions. The market setback after the news became public was led by heavy selling in the missile, electronic and aircraft groups.

Whether or not these meetings will result in substantial cutbacks in the arms race, and therefore affect the earnings of companies dependent on military spending, cannot be known at this time. It is, however, within the realm of possibility that some progress may be achieved, if not this

Fall, perhaps as a result of some future conference, so that similar market reactions in the future remain a distinct possibility. Investors may, therefore, want to think in the direction of commitments in those industries not dependent upon military spending as an important source of revenue.

This month's comments discuss three firms which offer the investor a means of participation in the economic growth of the country, whether it be based on defense preparedness or peace-time prosperity. The shares of James Talcott represent an interesting means of benefiting from a relatively new idea in an old industry—factoring. A fast growth and expansion minded retail chain, Interstate Department Stores, is expected to turn the earnings corner this year and the future looks bright. Interchemical Corporation, with a strong competitive position in the chemical coatings industry and excellent earnings and dividend history, rounds out this month's presentation of securities which, we feel, possess above-average potential.

JAMES TALCOTT, INC.

The shares of James Talcott at current levels appear attractively priced in relation both to current earning power and future prospects. For this year, we are estimating earnings in the $3.20-$3.40 a share range as compared with $2.63 in 1958. Furthermore, the present sharp gains in receivables fairly well assures another increase in net income next year. A dividend increase from the current $1.32 annual rate is a distinct possibility. We recommend the stock for investors primarily interested in growth coupled with capital gains possibilities.

James Talcott until 1944 was primarily an "old line factor" serving the textile industry. While the company had been successful and in business since 1854 growth was slow. In 1944 the company decided to diversify its operations to become a supplier of working capital funds to all industries. This resulted in the formation of the Commercial Finance Division and later the Industrial Time Sales Division. By offering a wider range of financial service to many industries and clients, Talcott's two new divisions have accounted for the rapid growth in the postwar period.

The company's three principal divisions are as follows:

1. *The Commercial Finance Division*—This division principally supplies revolving capital funds to borrowers during periods of growth or adjustment, including acquisitions and mergers, when funds are not available in sufficient quantity from banks or when equity or institutional financing is not feasible. Funds are usually made available against the security of accounts receivable. Receivables are assigned with full recourse. This division also makes additional funds available on short-term loans, secured by inventories, finished products, machinery and other fixed assets. This division has been a major contributor to Talcott's growth in the past eight years. In the fiscal year ended December 31, 1958, total receivables processed by this division aggregated $506,977,000.

2. *Factoring Division*—This division purchases accounts receivables without recourse, thus guaranteeing its clients against any loss. Along with assuming the credit risk, Talcott does the credit checking, collecting, ledg-

ANALEPTONE

RESTORATION OF FACULTIES AND BODY TON

The mutual synergic relationship between mental perce
tions of all kinds and body tone has been demonstrate

The combined central nervous and peripheral acti
of ANALEPTONE improve *both* mental faculties and bo
tone. These actions commend its use in a wide range
disorders common to aged patients.

CEREBRAL HYPOXIA CONFUSION
APATHY ANTISOCIAL BEHAVIOR
DEPRESSION LOSS OF MEMORY
INABILITY TO CONCENTRA

NOTE: No side effects are observed save for occasional and trans
"niacin flush" in sensitive individuals.

1. Boernstein, W. S.: Tr. New York Acad. Sci. *20*:72, 1957.

ADDITIONAL REFERENCES: Smigel, J. O.: M. Ti
85:149, 1957; Levy, S.: J.A.M.A. *153*:1260, 1953; Thompson, L
and Procter, R. C.: North Carolina M. J. *15*:596, 1954; Er
H. J.: Missouri Med. *53*:1071, 1956.

R&C **REED & CARNRICK**
Jersey City 6, New Jersey

ANALEPTONE ELIXIR

Each teaspoonful (4 cc) contains:

Pentylenetetrazol	200 mg.
Niacin	100 mg.
Peptenzyme® Elixir	q.s.

SUPPLIED: Bottles of 8 fl. oz.

ANALEPTONE TABLETS

Each tablet contains:

Pentylenetetrazol	100 mg.
Niacin	50 mg.
Pepsin 1:10,000	5 mg.

SUPPLIED: Bottles of 100.

DOSAGE: One-half to one teaspoonful of Elixir; one to two tablets, 1 to 3 or 4 times daily.

ering and other related clerical operations. The factored company, when it sells its accounts receivable, does not receive payment until the due date of the accounts sold. However, prior to the due date the factored company may draw an amount up to 90% of the net value of the receivables sold. Thus, the factor has two sources of income: (1) commissions received for credit checking and collection and (2) interest on funds advanced. Outstanding purchased receivables and loans to factored companies totaled as of December 31, 1958, $46,366,000.

3. *Industrial Time Sales Division*—This division purchases, from dealers and others, installment paper connected with the sale of income-producing equipment. This division also offers rediscount credit lines to auto finance firms, small loan companies and consumer finance organizations. The company does not directly finance consumer purchases.

Talcott operates these three divisions through four main offices (in New York, Chicago, Detroit and Boston) and representatives and correspondents in 30 principal cities.

The Factoring Division in general is non-competitive with commercial banks. While a few banks in certain geographic areas do offer factoring services, the overall impact is slight. The Commercial Finance Division is definitely non-competitive since it is basically used as a supplement to bank credit. For example, when a company is going through a period of growth or readjustment and normal bank lines are not sufficient to meet its credit needs, Talcott is usually asked to participate. Another important area for referrals is from investment banking houses. Talcott is used to supply intermediate-term credit until either a debt or equity financing can be accomplished.

Industrial time sales, on the other hand, are in direct competition with services offered by commercial banks. However, while being at a disadvantage as far as interest rates are concerned, Talcott has been able to compete effectively by offering specialized services and extremely flexible financing plans.

Volume of receivables purchased or financed in periods of tight money, such as the present, tend to increase at faster than normal rates. Many companies in a good business period find that their normal sources of working capital funds are not sufficient to fully capitalize their potential and thus come to companies such as Talcott. This situation exposes many new companies to Talcott's diversified financial services. What's more, experience has been that new customers tend to stay with the company, even after money gets easier, to avail themselves of the financial and other services offered.

Of course, as money gets tigher, Talcott's borrowing costs increase. However, in both the Commercial Finance and Factoring Divisions, the company passes on increased interest costs to the customers. In the Industrial Time Sales Division, where receivables have maturities of 12 to 48 months, the company is unable to pass on increased money costs. Nevertheless, they are still able to hedge against rising money costs by adjusting their capital structure so that industrial time sales are offset by fixed long-term debt and capital equity.

Total receivables acquired this year to June 30th totaled $496 million, a gain of 29% from $385 million

JAMES TALCOTT, INC.

Price	44
Dividend	$1.32
Yield	3%
Range	44¾-29
Traded	N.Y.S.E.

Capitalization (6/30/59)	
Long-term debt	$28,406,668
Pfd. stock ($50 par)	3,263,500
Common ($9 par)	950,507 shs.

in the similar period of 1958. Net income for the 6 months increased at a faster rate to $1,516,051, a gain of 51% from the $1,004,008 reported in 1958. On a per-share basis, after preferred dividend requirements, earnings were $1.49 on 950,507 shares outstanding as compared with $1.16 in the first six months of 1958 on a lesser number of shares outstanding.

All divisions participated in the excellent six-month gain. For example, while the Factoring Division increased volume 26%, it reported a gain of 72% in pre-tax income. This Division, of course, as was clearly evident by the figures, was able to handle a much larger volume without a corresponding increase in expense. Also, the Industrial Time Sales Division was able to report a doubling of volume and pre-tax income. The Commercial Finance Division showed a 21% gain in volume and 27% in pre-tax income.

Furthermore, it is our opinion that the gains of the first half will continue for the rest of the year. All indications such as unearned discount, receivables on the books and overall economic conditions point to a higher second half. We are estimating that the company will top $1 billion in receivables processed for the full year and earn about $3.20-$3.40 and possibly higher.

The company in recent years as it broadened its services has followed an active acquisition policy to gain additional receivables and personnel. Last year, Talcott acquired three companies which at year-end accounted for about 10% of funds in use. The company has stated that it will continue to follow a policy of acquisition.

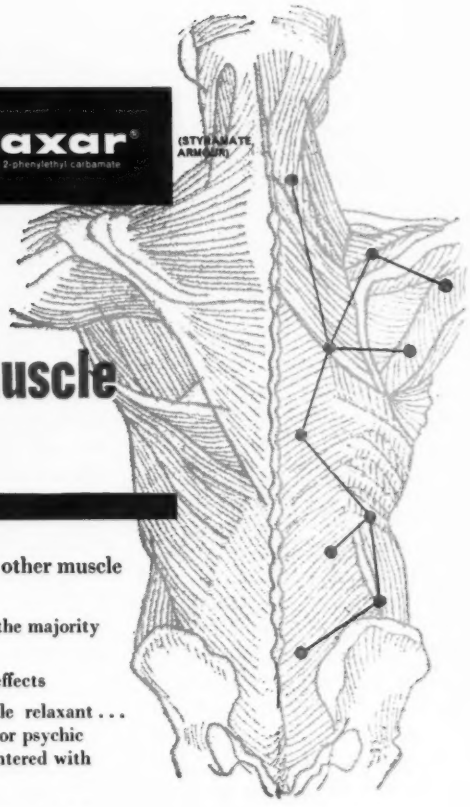
Net losses which may be incurred by the company in its operations can be attributed to two causes: (1) general credit losses resulting from the insolvency of the borrower or (2) losses on factored receivables purchased outright without recourse. In its factoring division the company charges a commission for assuming the risk of insolvency on receivables purchased outright as well as for the credit and collection work involved. The reserve for loss as of year end 1958 amounted to $2,130,000, and as of June 30, 1959 stood at $2,450,000.

INTERSTATE DEPARTMENT STORES

Interstate Department Stores has embarked on an expansion program which promises to materially lift earning power and to virtually double the 1958 volume of the company—all without recourse to outside financing and without dilution of stockholders' equity. This, combined with the recovery taking place in earnings derived from Interstate's original nucleus of stores, makes the shares look unusually cheap based on anticipated 1959 net of around $4.25 and cash flow of approximately $6.75 per share. Current annual cash dividends of $1.20 provide a yield of 3.8% to which is added 3% in stock

rely on

Sinaxar®
2-hydroxy 2-phenylethyl carbamate
(STYRAMATE, ARMOUR)



a specific skeletal muscle relaxant

Chemically unlike any other muscle relaxant, Sinaxar is

- consistently effective in the majority of cases
- long acting: no fleeting effects
- purely a skeletal muscle relaxant . . . free of adverse physical or psychic effects frequently encountered with tranquilizers

DOSAGE: *Two tablets three or four times daily.*

SUPPLIED: *200 mg. tablets in bottles of 50.*

INDICATIONS: Any condition involving skeletal muscle spasm, as ***musculoskeletal disorders:*** acute and chronic back ache; arthritides; bursitis; disc syndrome; fibrositis; myalgia; myositis; osteoarthritis; following orthopedic procedures; rheumatoid arthritis; spondylitis; sprains and strains; torticollis; ***neurologic disorders:*** cerebral palsy; cerebrovascular accidents; cervical root syndrome; multiple sclerosis.

ARMOUR

ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS
A Leader in Biochemical Research

The cash payment could be liberalized at year end.

Sales of this chain of junior department stores ($65.7 million in 1958) have been relatively static with earnings declining in recent years due to a continuing contraction of profit margins. Last year's per share earnings of $2.06 marked a 10 year low in net income reflecting the heavy dependence of approximately 60% of Interstate's midwestern stores on the depressed automobile industry. The worst appears to be over in this repect. The fourth Christmas quarter of 1958 was one of the most profitable in Interstate's history and permitted the company to end the year with $2 in earnings per share (adjusted for a 3% stock dividend), despite a loss in the first nine months. The improvement has continued thus far this year and it is currently expected that 1959 earnings from this source should recover to the $3 level or better with recent acquisitions bringing total earnings to $4.25 this year, with $5.00, and $5.50 per share estimated for 1960 and 1961, respectively.

In April of 1959, Interstate made the first of a series of moves which should reduce its heavy reliance on a few highly cyclical industrial areas. Acquisition of White Front Stores of Los Angles, a two-unit discount hard goods operation, with a $21 million volume and after-tax earnings of $558,000 was accomplished on a favorable—mostly cash—basis.

White Front should contribute about $1.25 conservatively to 1959 results (adjusted for the larger number of shares outstanding) and will form the nucleus of additional units beginning with two in the Los Angeles area probably within 8 to 18 months. It is currently planned that the two additional Los Angeles units would be in the $15 million annual volume category each. The company plans to broaden the merchandise handled by these stores by adding soft goods to the primarily hard lines now carried. In this instance, as well as in the next step to be outlined below, the combined experience of Interstate and White Front management should prove rewarding in an area which has sometimes been a stumbling block to merchants seeking to diversify their lines without the accumulated experience necessary to compete effectively in new areas.

The next step will be construction of the first two or a series of low-overhead mass merchandising stores ranging in size from 50,000 to 75,000 square feet and averaging about $5 million annually in volume. These units will be operated under the name "Family Fair," the first two will be opened in August and October of this year in Canton and Toledo, Ohio with two more following in the spring of 1960 in Louisville, Kentucky.

All told, the plans outlined above have the potential of lifting volume from 1958's $66 million to a level of $125-130 million within two or three years. At such a level, it is not difficult to foresee earnings of $5.50-$6.00 a share or better. (It may be noted that the company's tax rate in recent years has averaged around 42% with the rate in the past two years lower due to the depressed state of earnings. Projections are based on a return to the average rate.) Management does not anticipate the need for any additional financing to carry out this program; funds will come from present cash earnings, depreciation (which amounted to $884,535 in 1958, or more than net earnings of $627,

INTERSTATE DEPARTMENT STORES

Price	37	Capitalization (1/31/59)	
Dividend	$1.20	Long-term debt	$4,978,212
Yield	3.3%	Common stock	325,608 shs.
1959 Price Range	38¼-28½		
Traded	N.Y.S.E.		

762) and the proceeds of sale of certain less profitable older units either as their leases run out or as opportunities for sale present themselves.

The company's current ratio as of January 31, 1959 was 3.5 to 1 and cash items were substantial. Long-term debt as of the same date amounted to 24% of the total capitalization which means there is considerable leverage involved in this situation particularly considering that there are also minimum annual rentals in the picture. The shares must therefore be considered as speculative in nature although the risks at current levels appear limited.

INTERCHEMICAL CORPORATION

Interchemical Corporation, in the six months ended June 30, 1959, reported record sales of $63.13 million along with record earnings of $1.58 per common share. In the like months of 1958, sales were $53.13 million while earnings were 82¢ per share. Furthermore, while the results for the full first half of this year were highly gratifying, it is important to note that second quarter earnings reached 95¢ per share or better than 50% more than the first quarter. Thus, allowing for a modest seasonal decline in the third quarter and a resurgency by the fourth quarter, full year earnings of $3.25 per share seem within reach. Furthermore, considering the excellent level of earnings achieved in the second quarter, we now believe that Interchemical is fully capable of producing earnings comfortably in excess of $3.50 per share by 1960. (In 1958, Interchemical reported $2.15 per share.) The dividend, which has been raised at each of the last two meetings, is, in our opinion, likely to be raised at least once again within the next year.

Considering Interchemical's strong competitive niche, its excellent earnings and dividend history, its strong financial condition and its bright near and longer term outlook, we continue to regard these shares as undervalued at less than 12 times estimated 1959 earnings.

Broadly categorized, Interchemical is a producer of chemical coatings. It commands an extremely strong competitive position in printing and gravure inks where it probably controls 30%-40% of the total market. The company also produces industrial finishes, textile colors, adhesives, inked ribbons and polyester resins. Interchemical is essentially a compounder of finishes, makes few raw materials and does not sell directly to end use consumers although it is tied closely to the latter group through its industrial customers.

Approximately 38% of 1958 sales of $109 million went to the packaging industry, which is Interchemical's largest and fastest growing customer industry. The company's inks and coatings are used on boxes, cans, plastic containers, bags, wrappers and drums. The packaging industry, abetted by the revolution created by

self-service retail distribution, has enjoyed tremendous prosperity in the postwar period. This industry in 1958 was reported to have accounted for sales of $16 billion and is growing at a rate of approximately 10% per year or about three times the growth rate of the U.S. economy as a whole. Everyone who shops must be fully aware of the tremendous myriad of packaging containers that have been developed since the food industry turned to self-service in the now familiar supermarket. This revolution is currently proceeding rapidly not only within the supermarket, but also among department, hardware, haberdashery and other types of retail outlets. Of special interest is the tremendous growth in the use of plastic films. Demand for polyethylene as a film packaging material is expanding at a rate above 20% per year, to say nothing of continued good demand for cellophane, vinyls, polyesters and other types of wrapping materials. Furthermore, traditional industrial containers such as corrugated boxes and steel drums now are printed and colored for advertising benefits. The advent of large-scale color television, moreover, should further accelerate the demand for color advertising.

Interchemical's second largest customer industry is newspaper and magazine publishing which, in 1958, accounted for 15% of total sales. About 50% of magazine advertising is now printed in color with this proportion expected to improve as color television's impact is felt on a broader scale. In the case of newspapers, traditional inks (newsblack) still dominate but here again, the use of color is growing as the use of preprinted color advertising inserts expands. Rising use of color as against black inks in newspaper and magazine publishing is quite beneficial to Interchemical since the colored materials carry higher price tags and better profit margins. About 20% of the company's new ink sales in 1958 came from these colored materials.

The balance of the company's sales (47%) is divided among a great variety of industries such as printing and lithography (10%); textile, leather and plastic converting (14%); household furnishings (3%); transportation equipment (3%); and miscellaneous (17%). Thus, Interchemical's outlets are sufficiently diversified to avoid undue operating fluctuations. At the same time, these various industries offer the company an excellent opportunity to perform the job it knows best—i.e., provide high quality chemical coatings and thus exploit its position in a highly important field suited only for the qualified specialist.

Reflecting these elements of growth, Interchemical has expanded its sales from $69.5 million in 1949 to $109.5 million in 1958, a gain of 58.5%. (However, adjusted for the elimination of the company's unsatisfactory consumer products division some years ago, the percentage growth in sales of present lines in the past 10 years would show an 84.4% rise.) Net income before Federal income taxes during these years jumped from $3.49 million to $9.59 million, a gain of 174% indicating an actual improvement in profit margins. This factor, of course, is a tribute to management capabilities since improved productivity in the postwar period has not been commonplace due primarily to the general cost-price squeeze. Of greatest significance to

u can expect
ur patients
th low back pain
return to
rmal activity
en you prescribe

Trancopal

e profile no. 2758

iddle-aged man had intermittent low back pain that he attributed to injuries received in an automobile
ent three years previously. The pain radiated down both legs, making the patient walk bent over. He also
ifficulty getting out of bed and had to pull his knees up and roll out. Any heavy lifting precipitated a
ttack, and he tired easily.

ings on x-ray of the thoracic and lumbar spine gave negative results. Findings from other laboratory
s were within normal limits. A herniated disc, although still a possibility, was temporarily ruled out
e neurologic examination. Previous treatment consisted of analgesics and steroids (without success), and
ics were given during severe attacks.

iving a dosage of Trancopal, 100 mg., three times a day, this patient is able to walk almost normally and
on his regular activities as long as he does not overexercise. He has been taking Trancopal over seven
s with excellent relief of symptoms. No side effects have occurred. *Clinical Report on file at the Department o*
Medical Research, Winthrop Laboratories.

INDICATIONS: Musculoskeletal: Low back pain (lumbago, sacroiliac pain); neck pain (torticollis, etc.); bursitis; rheumatoid arthritis; osteoarthritis; disc syndrome; fibrositis; ankle sprain; tennis elbow; myositis; postoperative muscle spasm.
Psychogenic: Anxiety and tension states; dysmenorrhea premenstrual tension; asthma; angina pectoris; alcoholism
Dosage: 100 to 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.
Supplied: Trancopal Caplets® 100 mg. (peach colored scored), bottles of 100.

Trancopal®

first true TRANQUILAXANT

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S. Pat. Off.

Winthrop LABORATORIES • New York 18, New York

INTERCHEMICAL CORPORATION

Price	39¾	Capitalization (6/30/59)	
Indicated Dividend	$1.40	Long-term debt	$3,720,000
Yield	3.6%	4½% pfd. ($100 par)	71,622 shs.
1959 Price Range	40¼-27½*	Common ($5 par)	2,024,319 shs.
Traded	N.Y.S.E.		

(*) Adjusted to reflect 2½ for 1 split April 1, 1959

the common stockholder is the fact that earnings on a per share basis have more than doubled from $1.04 per share in 1949 to $2.15 in 1958 with $3.25 projected for the current year. The dividend rate, which has never been reduced in the postwar period, has been increased seven times since 1949 with further increases now likely. Non-cash depreciation charges have also doubled from around $1.0 million in 1949 to over $2.0 million or about $1.14 per share last year.

In order to expand production facilities and improve efficiency, capital expenditures in recent years have been relatively high. In the latest four-year period, 1955-58, these expenditures totaled over $13 million compared with only $7 million in the previous four-year period, 1951-54. Despite these large expenditures, Interchemical's financial condition remains very strong. On June 30, 1959, current assets were $42 million while current liabilities were $13.4 million. Current assets included more than $9 million in marketable securities which the company intends, in time, to use for further expansion or possible acquisitions as favorable opportunities arise. Long-term debt represented by 3⅛% promissory notes maturing in 1963 stood at a modest $3.72 million. Return on stockholders' invested equity has averaged 14.1% in the last four years which is slightly above average for the chemical industry as a whole and comfortably above the average of all industrial corporations.

These favorable elements relating to Interchemical's operating history and financial condition should not, in our judgment, be overlooked in evaluating the company's investment standing.◄

NEW PHARMACEUTICALS

Marplan *(Roche)*

Amine oxidase regulator, anti-anginal and antidepressant. *Indications:* For prophylaxis of pain in angina pectoris, especially in patients unresponsive to conservative management. In a variety of psychiatric disorders with associated symptoms of depression, withdrawal or regression. As adjunctive therapy in rheumatoid arthritis and other chronic debilitating disorders with associated depressed psychomotor activity. *Dosage:* As directed by the physician. *Supplied:* Tablets, each containing 10 mg. of isocarboxazid, in bottles of 100 and 1000.

Mepergan-50 *(Wyeth)*

Each cc. contains 50 mg. of promethazine and 50 mg. of meperidine. *Indications:* In obstetrics, all forms of surgery, and in severe pain, including the pain of malignancy. *Dosage:* As directed by the physician. *Supplied:* Multiple-dose vials and disposable sterile-needle units. Also available in lower concentration, each cc. contains 25 mg. of promethazine and 25 mg. of meperidine (Mepergan-25).

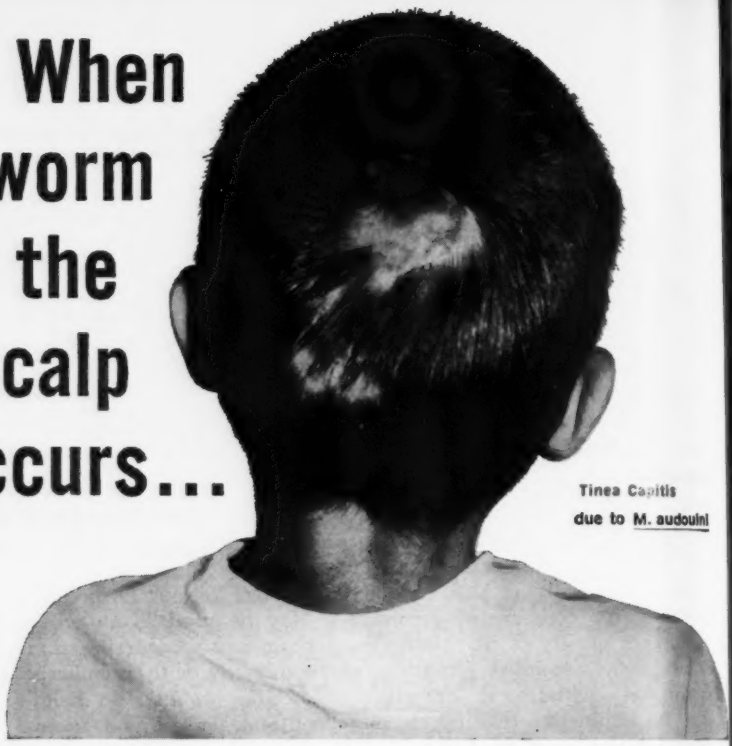
Vanay *(Ayerst)*

Vaginal cream containing 250 mg. of glyceryl triacetate per gram in a nonliquefying base. *Indications:* Antifungal therapy in monilial vaginitis. May be used as an adjunct in trichomoniasis occurring alone or concomitantly with moniliasis. In nonspecific vaginitis, to help restore a physiologic pH and normal vaginal flora. *Dosage:* Average dose is 2 to 4 grams intravaginally at bedtime. During acute stage, apply twice a day, morning and night. *Supplied:* Combination package: 1½ ounce tube with 15 disposable applicators, calibrated at the level of 2, 3 and 4 grams.

Depo-Medrol *(Upjohn)*

Each cc. contains 40 mg. of methylprednisolone acetate suspended in sodium chloride injection with suitable suspending and preservative agents. *Indications:* Locally for intra-articular, intrabursal, intratendinous and intralesional therapy. Systemically it is administered intramuscularly and by continuous drip for intrarectal administration. *Dosage:* As directed by the physician. *Supplied:* In 1 cc. and 5 cc. vials.

When ringworm of the scalp occurs...



Tinea Capitis
due to M. audouini

...topical antifungal therapy is recommended as immediate treatment. Prom
se of Salundek will destroy accessible spores and form a protective coating, reducing th
kelihood of spread of the disease to other areas of the scalp, or to other children.

*lew Dosage Form, Salundek Solution** — It is supplied in 3-ounce bottles with a controlle
ow applicator cap. Now there is a choice that will lead to better patient cooperation durin
he treatment of this stubborn disease.

Many investigators have reported that the ointment and the solution have the same hig
ercentage of cures, obtained in an average of 12 to 16 weeks.

alundek also eliminates the hazard of x-ray therapy • seldom causes skin reaction • offe
onvenience in use — no stain, no odor and no effect on future hair growth.

upplied: SALUNDEK OINTMENT, 2 oz. tubes and 1 lb. jars. SALUNDEK SOLUTION, 3 o
ottles with controlled flow applicator cap.

Write for supply of "Instructions for Home Care" pads.

SALUNDEK®

OINTMENT
SOLUTION

(Brand of Zinchlorundesal)

Maltbie

MALTBIE LABORATORIES DIVISION • Wallace & Tiernan Incorporated • Belleville 9, N.

In the presence of open lesions, the use of the ointment may be preferred at first since the base of the solution ca
occasional transient stinging. Avoid contact with the eyes.

Grifulvin *(McNeil)*

Antifungal antibiotic for oral administration. Each tablet contains 250 mg. of griseofulvin. *Indications:* Active specifically against superficial fungi that cause tinea of the scalp, beard, body, hands, feet, fingernails and toenails. *Dosage:* As determined by the physician. *Supplied:* In bottles containing 16 or 100 tablets.

Decabamate Tablets
(Merck Sharp & Dohme)

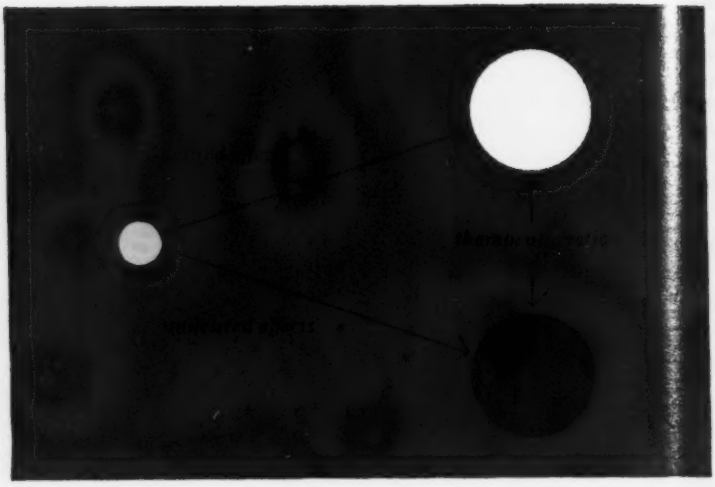
Each tablet contains 0.25 mg. of dexamethasone and 200 mg. of meprobamate. *Indications:* In the treatment of allergic and inflammatory conditions where apprehension, tenseness and anxiety and other emotional components are part of the condition being treated. In asthma, arthritis, neurodermatitis, muscle stiffness, spasm, pain and ache accompanying major involvement (low back pain, bursitis and synovitis). *Dosage:* For oral administration as directed by the physician. *Supplied:* In bottles containing 100 tablets.

Surfak *(Lloyd)*

Change in name. Formerly called *Doxical. Indications:* Wherever a fecal softener is indicated for the treatment of constipation. *Dosage:* As directed by the physician. *Supplied:* In bottles containing 100 capsules.

Nitretamin-10 *(Squibb)*

New potency form. Each tablet contains 10 mg. of triethanolamine trinitrate diphosphate. *Indications:* For preventing or reducing the severity of attacks of angina pectoris. *Dosage:* One tablet twice a day. *Supplied:* In bottles containing 50 tablets.



The best therapeutic ratio in the steroid field confirmed by a comparative clinical study of

prednisone
prednisolone
methylprednisolone
triamcinolone
dexamethasone

in 65 rheumatoid arthritis patients:

". . . It would appear from these comparative observations that methylprednisolone [Medrol] probably is the steroid of choice for initial trial in a patient with rheumatoid arthritis. It is potent, and displays a slightly improved 'safety' record, showing a reduced frequency of disturbing side effects compared with the other steroids."[1]

Medrol

TRADEMARK, REG. U.S. PAT. OFF. — METHYLPREDNISOLONE, UPJOHN

. . . hits the disease, but spares the patient

1. Neustadt, D. H.: Corticosteroid Therapy in Rheumatoid Arthritis: Comparative Study of Effects of Prednisone and Prednisolone, Methylprednisolone, Triamcinolone, and Dexamethasone, J.A.M.A. 170:1253 (July 11) 1959.

Upjohn

Niamid *(Pfizer)*

Antidepressant agent and mood brightener. Each tablet contains 25 mg. of nialamide. *Indications:* For the treatment of psychotic and psychoneurotic depression, as well as other disease states in which depression is an important symptom. As adjunctive therapy in angina pectoris. *Dosage:* Suggested initial dosage is 75 mg. daily for a week or more. Dosage may then be revised according to response. *Supplied:* In bottles containing 100 tablets. Also available in 100 mg. tablets, bottles of 100.

C-B Vone Capsules *(U.S. Vitamin)*

Broad spectrum nutritional formula. *Indications:* To help keep patients more vigorous and healthier. To replenish stress-depleted vitamin levels. *Dosage:* One or two capsules daily as needed. *Supplied:* In bottles containing 15, 30, 50, 100 or 500 capsules.

Betadine Ointment *(Tailby-Nason)*

Topical pathogenicidal agent. The active ingredient is povidone-iodine. *Indications:* For mycotic and bacterial skin infections and other skin conditions where infection threatens. *Dosage:* For topical application as directed by the physician. *Supplied:* In 1 ounce tubes.

Robaxin Injectable *(Robins)*

Each ampul contains 1 gm. of methocarbamol in a 10 cc. sterile, 50% aqueous solution of polyethylene glycol-300. *Indications:* For relief of the acute phase of skeletal muscle spasm. *Dosage:* To be determined by the physician. *Supplied:* As 10 cc. ampuls in packages containing 5 or 25 ampuls.

Fulvicin *(Schering)*

Antifungal antibiotic for oral administration. Each tablet contains 250 mg. of griseofulvin. *Indications:* Active specifically against superficial fungi that cause tinea of the scalp, beard, body, hands, feet, fingernails and toenails. *Dosage:* As determined by the physician. *Supplied:* In bottles containing 30 tablets.

Temaril Spansule Capsules, 5 mg. *(S.K.F.)*

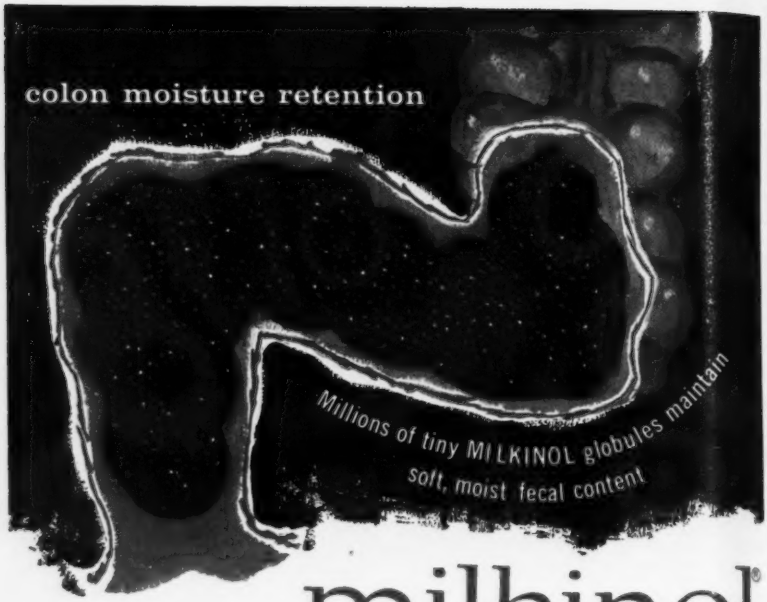
New dosage form. Each sustained release capsule contains 5 mg. of trimeprazine. *Indications:* Oral medication with specific antipruritic activity in a wide variety of conditions. *Dosage:* One capsule every 12 hours, for adults. *Supplied:* In bottles containing 30 capsules.

Chymar Buccal Tablets *(Armour)*

Tablet form of the systemic anti-inflammatory enzyme, chymotrypsin. *Indications:* To prevent or relieve inflammation, reduce swelling and pain, promote healing. *Dosage:* As directed by the physician. *Supplied:* In bottles containing 24 tablets.

Oretic *(Abbott)*

Oral diuretic, antihypertensive. Available in two strengths: Each tablet contains either 25 *or* 50 mg. of hydrochlorothiazide. *Indications:* In the treatment of renal and cardiac edema. In the management of toxemia of pregnancy, premenstrual tension and steroid edema. In the management of the majority of cases of hypertension. *Dosage:* To be directed by the physician. *Supplied:* Either strength, in bottles containing 100 or 1000 tablets.



milkinol®

non-habit forming constipation correctant

Milkinol, a unique aqueous-mixing liquid petrolatum, assures soft, moist fecal content by retaining colon moisture balance—solves the constipation problem for all age groups, even chronic constipation of long-standing.

Uniform retention of Milkinol within the fecal mass avoids leakage. There is no interference with nutrition or vitamin absorption when taken as directed.

Very pleasant —mix with just a few swallows of any drink you prefer.

Convince yourself, Doctor milkinol *is the modern constipation correctant that solves the problem for all age groups.*

Send for samples and literature today

Prescribe with Confidence

KREMERS URBAN COMPANY

Milwaukee 1, Wisconsin — Ethical Pharmaceuticals Since 1894

Ciba Foundation Symposium on the Regulation of Cell Metabolism

editors for the Ciba Foundation G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Cecilia M. O'Connor, B.Sc. With 109 illustrations. Little, Brown and Company, Boston. $9.50

This 350 page report of the Proceedings of the Symposium represents the most comprehensive dealing possible with a subject, perhaps the most fundamental in the realm of human knowledge. It would be largely futile to attempt to give anything more than a meager idea of the scope of the program. Among the subjects discussed in the presentation are: Rate Limiting Factors in Cell Respiration, On the Meaning of Intracellular Structure for Metabolic Regulation, Control of Rate of Intracellular Respiration, Some Problems in the Choice of Oxidative Pathways of Carbohydrate Metabolism, Alternative Pathways of Electron Transport, Enzymic Regulation of Fermentation in Yeast Cells, Mechanisms for Control of Enzyme Synthesis and Enzyme Activity in Bacteria, Automatic Adjustment Mechanism in Bacterial Cells, and Regulation of Growth and Composition of the Bacterial Cells.

One can see at a glance, indeed could see from the very title of the book, that the dealing is with the deep things of life.

Fundamentals of Otolaryngology: A Textbook of Ear, Nose and Throat Diseases

by Lawrence R. Boies, M.D., University of Minnesota Medical School. Third Edition. Illustrated. W. B. Saunders Company, Philadelphia. 1959. $8.00

Despite the necessity of including the great number of important developments in this field, the volume has been held to practically the size of the first two editions. The purpose of the book of offering only fundamental information to the undergraduate medical student or the nonspecialist physician has been steadily kept in mind. Three additional chapters have been added to outline the fundamentals of reconstructive nasal surgery, maxillofacial surgery of tumors and injury, and tumefactions of the neck other than those of the thyroid gland.

Practical Dermatology, Second Edition

by George M. Lewis, M.D., F.A.C.P., Professor of Clinical Medicine (Dermatology), Cornell University Medical College. W. B. Saunders Company, Philadelphia. 1959. $8.00

The first edition of this book met with enthusiastic welcome by the medical students and the general practitioners for whom it was written, as attested by the demand for the second edition. Those who have been looking forward to an appearance of this edition will not be disappointed. The essentials of all the common, and many of the uncommon, skin diseases are presented clearly, without wastage of words or display of erudition. The illustrations are many and excellent.

Viral and Rickettsial Infections of Man

edited by Thomas M. Rivers, M.D., Member Emeritus, The Rockefeller Institute, Vice-President-Medical Affairs, The National Foundation and Frank I. Horsfall, Jr., M.D., Vice-President for Clinical Studies, Physician-in-chief to the Hospital, The Rockefeller Institute. Third edition—134 illustrations. The J. B. Lippincott Company, Philadelphia. 1959. $8.50

The microbial agents included in these two groups differ greatly from one another, but all have some features in common. They are very minute, reproduce only in living cells, and those considered here are capable of causing disease. Great advances in our knowledge of these infections in the 6-year period since publication of the 2nd edition of this book. Several new groups of viruses of importance have been discovered and the recognition of their relation to a variety of infectious processes has proceeded apace. This edition is the work of 44 contributors, all selected because of their large experience in this field of investigation and their especial fitness. Three of the seven new chapters deal with common features of viruses and infections they cause; two others deal with groups of viruses discovered since this previous edition appeared—ECHO and Adeno—viruses. The book is designed to provide full information on viral and rickettsial infection which will meet the needs of graudate students of biology, including those preparing for a career in medicine, and for the use of physicians, teachers and investigators in the biological sciences. It seems that it will serve its purpose admirably.

Practical Note on Nursing Procedures

by Jessie D. Britten, S.R.N., Sister Tutor Diploma (London). Trained at Royal Free Hospital. Sister Tutor, Worcester Royal Infirmary, Examiner to the General Nursing Council for England and Wales. Foreword by George H. Marshall, F.R.C.S. (Edin.), Worcester Royal Infirmary. Second Edition. E. & S. Livingstone Ltd., Edinburgh & London. Williams & Wilkins Company, Baltimore. 1959. $4.00

The book lives up to the claim of being "practical," confining itself to supplying information which, put into practice, will make an excellent nurse.

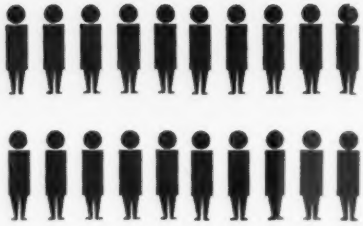
FOR UNMATCHED TOLERANCE AND OPTIMAL ABSORPTION

MOL-IRON + VITAMIN C

(Molybdenized-Ferrous Complex)

IN IRON DEFICIENCY ANEMIA — SPECIALLY WHEN IRON ABSORPTION IS DEFECTIVE

MOL-IRON
WELL TOLERATED
by **97.9%**
of 336 patients[1-9]



But 22.4% G. I. side effects with $FeSO_4$

VITAMIN C — "Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid..."[10]

MOL-IRON WITH **VITAMIN C** TABLETS

Each contains — Mol-Iron (ferrous sulfate 195 mg., and molybdenum oxide 3 mg.) plus ascorbic acid 75 mg. Bottles of 100. Dose—1 or 2 tablets t.i.d.

1. Brit. M. J. 1:407, 1952. 2. Bull. Margaret Hague Mat. Hosp. 1:68, 1948. 3. Am. J. Obst. & Gyn. 57:941, 1949. 4. Connecticut M.J. 14:930, 1950. 5. J.-Lancet 66:218, 1946. 6. Am. J. Obst. & Gyn. 62:947, 1951. 7. Am. J. Med. Sc. 212:76, 1946. 8. Obst. & Gynec. 5:201, 1955. 9. J. Ped. 41:170, 1952. 10. Ann. Int. Med. 42:458, 1955.

WHITE LABORATORIES, INC.
KENILWORTH, N. J.